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Cardiovascular adaptations to exercise training in older women with and without type 2 diabetes mellitus

by

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the

requirements for the degree of Doctor of Philosophy

Faculty of Physical Education and Recreation

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Abstract

Background: Aging and type 2 diabetes mellitus (2-DM) are associated with an increased risk for cardiovascular disease, likely due to left ventricular and vascular maladaptations associated with each condition. Exercise may attenuate these maladaptations and reduce CVD risk in these populations. To date however few investigations have examined the effects of exercise training on cardiovascular structure and function in these populations.

Methods: Three separate exercise training interventions were used to document the cardiovascular adaptation to exercise training in older healthy women (n= 35; Study I) and older women with 2-DM (n= 10 Study II; n= 14 study III). A fourth study was performed comparing novel and conservational markers of cardiovascular disease between two groups of women with 2-DM (n = 28) stratified according to their level of cardiorespiratory fitness. Left ventricular filling dynamics and arterial stiffness were assessed non-invasively from Doppler-derived transmitral flow patterns and pulse contour wave analysis respectively. Exercise training consisted of aerobic and resistance training 3 times per week for a period of 10 (studies II & III) or 12 weeks (study I). Cardiorespiratory fitness was assessed from measurement of rates of oxygen consumption during a graded maximal exercise test to exhaustion.

Results: In study I, exercise training was associated with an improvement in cardiorespiratory fitness despite no change in left ventricular filling dynamics. In study II and III, exercise training elicited improvements in arterial compliance secondary to improvements in cardiorespiratory fitness in women with 2-DM. Similar to study I, no changes in LV filling dynamics were observed in women with 2-DM studies II and III. In

study IV low cardiorespiratory fitness was associated with an increase in C-reactive protein and a reduction in insulin sensitivity in women with 2-DM.

Conclusions: Exercise training is associated with improvements in cardiorespiratory fitness in older women with and without 2-DM, despite no measurable change in LV filling dynamics. Exercise training is associated with an improvement in arterial compliance in women with T2D despite independent of changes in classical markers of CVD.

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List of abbreviations

1-RM – One repetition maximum

DM-2 - type 2 diabetes mellitus

ACF – average cardiorespiratory fitness

AMPK – 5`-AMP activated protein kinase

AT – aerobic trained

CIMT – carotid intima-media wall thickness

CmT – Combined training

CRP – C-reactive protein

CT – Control

CVD – Cardiovascular disease

ECG - electrocardiogram

ET – exercise trained

HbA_{1C} – glycosylated hemoglobin

HDL – high density lipoprotein

HOMA – Homeostasis model assessment of insulin resistance

LCF – low cardiorespiratory fitness

LDL – Low density lipoprotein

LV - left ventricular

ST – strength trained

TG – triglyceride

VO_{2max} – maximal rate of oxygen consumption

VO_{2peak} – peak rate of oxygen consumption

Definitions

Compliance = This term is used to describe the change in pressure for a given change in volume.

Endothelial function = Ability of the endothelial layer to release nitric oxide, causing vasodilation.

Diastolic function = Left ventricular performance during the diastolic phase of the cardiac cycle. This is typically estimated from Doppler-derived transmitral flow patterns.

Pseudonormalized = Refers to a transmitral filling pattern that appears to be normal, however is reversed when cardiac filling volumes are reduced (i.e. when the patient performs a valsalva maneuver)

Subclinical vascular inflammation = This is aterm used to describe a haematological state in which there is an increase in inflammatory markers associated with vascular disease.

VO_2Max = Maximal rate of oxygen consumption. This term is used to describe the maximal rate of oxygen consumption achieved during a graded exercise test to exhaustion. It is assumed that three of the following criteria have bene achieved to ensure a "maximl effort": (1) Maximal heart rate within 5 beats of age-predicted maximal value; (2) respiratory exchange ratio values greater than 1.15 at the end of the test; (3) an increase in rate of oxygen consumption of less than 150 mL/min with an increase in workload; (4) lactate value greater than 8.0 mMol/L upon completion of the investigation; (5) rating of perceived exertion greater than 18 on a Borg scale.

VO_2peak = Peak rate of oxygen consumption. This value is determined from the rate of oxygen consumption values acquired during the final 60 seconds of a graded maximal exercise test.

Chapter I. REVIEW OF LITERATURE

1. Introduction

One of the earliest descriptions of the beneficial role of exercise in the treatment of diabetes came from Aulus Cornelius Celsus (25 B.C.-50 A.D.) who stated: "But when the urine exceeds the quantity of fluid taken…it gives rise to wasting and consumption; if it is thin there is need for exercise… if it is thick, exercise... should be more thorough"[1]. These sentiments were echoed by Joslin[2] nearly two millennia later who suggested that exercise was beneficial to glucose homeostasis in patients with diabetes. In the seven decades since this statement was made, the role of regular exercise in the prevention[3] and treatment[4] of diabetes has become one of the most investigated areas in diabetes research. However, the advantages of regular physical activity in individuals with this disorder may have greater implications than initially proposed. Although glycemic control is an important therapeutic target for persons with type 2 diabetes (DM-2), the major of cause of morbidity and mortality in this population is cardiovascular disease (CVD).[5] As physical activity is associated with beneficial cardiovascular outcomes, exercise performed on a regular basis may be essential not only for metabolic control but also for the maintenance of a healthy cardiovascular system.

The Framingham Study was one of the initial investigations to demonstrate that diabetes was a primary risk factor for the development of CVD.[6] Since this time, a large number of studies have established the cardiovascular consequences of metabolic dysregulation in DM-2. The underlying mechanisms responsible for the increased risk of CVD associated with DM-2 have yet to be entirely determined. However, adverse changes in cardiac and vascular structure and function have been implicated in a number of recent investigations.[7,8]

In the healthy aging population, physical activity is considered the cornerstone of CVD prevention.[9] In contrast, relatively few studies have examined the cardiovascular benefits of regular exercise in persons with DM-2. Accordingly, the aim of this chapter is to document what is currently known regarding the impact of DM-2 on the cardiovascular system and to then address the potential role of exercise in preventing these unwanted adaptations.

2. Cardiovascular Consequences of Type 2 diabetes

2.1. Left Ventricular Maladaptations to Type 2 Diabetes

2.1.1 *Left Ventricular Morphology*

Reports over the past two decades have demonstrated deleterious alterations in left ventricular (LV) structure and function associated with DM-2, which have been defined as a non-ischemic diabetic cardiomyopathy.[10-12] Data from the Framingham[13] and Strong Heart[7] studies reveal that diabetics exhibit greater LV mass indexed to height as well as increased relative (i.e. wall thickness to cavity ratio) and absolute wall thickness. This type of LV remodelling is classified as a concentric hypertrophy and may explain the increased incidence of cardiovascular mortality and incidence of heart failure in persons with DM-2.[6,14,15]

Another relevant finding of both the Framingham and Strong Heart studies was the presence of gender differences with regards to LV adaptation in diabetes, as women exhibited slightly higher increases in LV mass relative to their glucose tolerant counterparts, than did men. Specifically, the Framingham study demonstrated that women with DM-2 displayed a significantly greater age-related increment in LV mass[13] while the Strong Heart Study revealed that the LV hypertrophy in DM-2 was significantly greater in women than in men[7]. These observations may explain why DM-2 in women is associated with a greater risk for CVD and heart failure than in men.[6,16]

2.1.2 *Left Ventricular Systolic Function*

In Grossman's model of LV hypertrophy, concentric hypertrophy is a necessary adaptation that normalizes wall stress associated with altered LV loading conditions. Concomitantly, it is usually associated with an augmentation in LV systolic performance. However, enhanced LV systolic function has not been reported in DM-2. On the contrary, large prospective investigations such as the Framingham and Strong Heart Study suggest that DM-2 is associated with a reduction in LV systolic function as fractional shortening was decreased compared to non-diabetic controls.[7,13] Although the differences reported in these studies were statistically significant, they were minimal and the physiological relevance may be limited.[7] However, even though differences in LV

systolic function were small, the impact of their findings is significant as the expected change in LV systolic function with concentric hypertrophy would be an enhanced contractility.[7,18]

Fang *et al.*[17] utilized novel markers of LV contractility (tissue Doppler estimates of myocardial peak strain and strain rate) to evaluate the impact of DM-2, concentric hypertrophy and the two combined on LV systolic function. DM-2 and concentric hypertrophy were independently associated with impaired LV contractility. Moreover, the reduction in LV contractility in patients with both DM-2 and concentric hypertrophy was significantly greater than in the groups with either condition alone. Interestingly, the common measures of LV systolic function, ejection fraction and fractional shortening, were similar between groups. Therefore, the authors suggest that more sensitive measures of LV systolic function, such as myocardial strain, should also be used to detect any changes in LV contractility associated with DM-2.

To accurately determine if LV systolic function is impaired in a diseased state, measurements should not only be taken at rest but during increased cardiovascular work. Hsu *et al.*[19] used stress echocardiography to evaluate LV systolic reserve during graded doses of dobutamine in patients with DM-2. Although, ejection fraction and velocity of circumferential fiber shortening at rest were not different between patients with DM-2 and age-matched controls, contractile reserve was reduced. Moreover, the reduced contractile reserve was exaggerated in subjects with microvascular disease. Sasso *et al.*[20] reported that persons with DM-2 showed normal LV ejection fraction at rest and a normal rise in ejection fraction during supine dynamic exercise. Both resting and exercise ejection fraction values were significantly lower than their non-diabetic peers. Furthermore, these authors report a significant correlation between insulin sensitivity and ejection fraction at rest and during exercise ($r = -0.59$ and $r = -0.58$, $p < 0.05$ respectively). Importantly, although ejection fraction values were lower in DM-2 across all conditions, they were always within normal limits. These findings add further support to the contention that the severity of the diabetic state might be an important factor in determining LV systolic function in DM-2.[21]

2.1.3 *Left Ventricular Diastolic Function*

The diastolic properties of the LV are intricate and difficulties associated with measuring LV performance during diastole make interpretation of results complicated. Ideally, invasive measures of LV pressures, coupled with estimates of LV volumes would provide a detailed description of LV compliance, however studies of this nature have yet to be performed in humans with DM-2. Instead, LV filling dynamics or more specifically, the ratio of early to late transmitral filling rate is commonly used to estimate LV function in diastole. More recently, the use of pulmonary venous profiles and a valsalva maneuver have also been used to uncover pseudonormalized transmitral filling patterns to describe altered LV function during various phases of diastole.[22]

Impaired LV filling dynamics are evident in approximately 50-60% of patients with DM-2.[22-25] This may be a conservative estimate as approximately 25% of LV filling profiles in middle aged DM-2 men are pseudonormalized.[22] The clinical concern is that impaired LV filling dynamics have been shown to be associated with adverse cardiovascular outcomes.[26] It is for this reason that the Doppler analysis of transmitral flow patterns and pulmonary venous flow should be considered in the screening of pre-clinical diabetic cardiomyopathy.[22] From a functional point of view, impaired resting LV filling dynamics have been shown to be associated with reduced exercise capacity in DM-2[23] and hypertension[26] and may explain, in part, the reduced exercise tolerance observed in these patients.

In healthy young individuals, approximately 2/3 of LV filling occurs passively due to an atrial-ventricular pressure gradient across the mitral valve, while the remaining 1/3 is supplied in late diastole from atrial contraction. The diabetic LV filling profile is associated with a decline in the passive component of filling coupled with an increased reliance on atrial contraction, thereby decreasing the ratio of early to late filling to < 1.[22-25] This pattern of LV diastolic filling is similar to that observed with normal aging, however it is exaggerated in DM-2 and is also associated with a pulmonary venous profile indicative of increased LV diastolic pressures.[22] Impaired LV diastolic filling dynamics observed in DM-2 have been shown to be independent of age, body weight and LV morphology.[24] Several mechanisms likely contribute to this altered LV diastolic filling, such as the presence of hypertension, increased collagen deposition, fibrosis or the development of advanced glycated end-products[28]. Furthermore, as LV filling

abnormalities are also evident in other diseases of metabolism such as obesity[29-31] and insulin resistance,[32,33] at least part of this dysfunction may be metabolic in nature.

The Strong Heart Study examined LV filling profiles in 3500 patients within American Indian communities in the United States.[24] Patients were stratified according to their degree of hypertension (hypertensive, mild hypertension, normotensive) and level of glycemic control. Both hypertension and DM-2 negatively impacted LV diastolic filling in an independent and additive manner.[24] In addition, among the type 2 diabetics, abnormal relaxation was associated with higher fasting glucose and glycosylated hemoglobin, which supports the notion that metabolic dysregulation may be a contributor to the impaired LV filling.

The impact of impaired systolic or diastolic function at rest is a concern as either may be worsened with increased LV workload. Interestingly, there is little correlation between LV systolic function at rest and exercise capacity, however resting LV filling dynamics have been shown to correlate well with cardiorespiratory fitness in healthy individuals.[34-36] If altered resting LV filling reflects a non-compliant LV in DM-2, this may attenuate the Starling-mediated increase in stroke volume with exercise.[37] In support of this, impaired LV diastolic reserve and reduced filling rates have been reported during exercise in type 1[38,39] and type 2 diabetic individuals[20], suggesting that the diabetic state is associated with a reduction in preload reserve and possibly the inability to use the Starling mechanism to increase cardiac output during exercise.

To our knowledge there are no investigations that have directly compared LV structure and function between aged and DM-2 populations, however both conditions are associated with concentric hypertrophy, reduced systolic reserve and more importantly reduced LV compliance. Levine *et al.*[40] suggest that age related changes in the LV end-diastolic pressure volume relationship are less a function of age and may be more a function of reduced levels of physical activity. As DM-2 is in large part a disease that develops secondary to a sedentary lifestyle, it is possible that the LV adaptations to DM-2 are also a function of physical inactivity. In that context it is possible that the LV adaptation to DM-2 may be reversed with increased levels of physical activity.

2.2 Vascular Maladaptations in DM-2

Vascular health is commonly assessed using several techniques, including morphological measures of intima-medial wall thickness, estimates of arterial compliance, and more recently, endothelial sensitivity to varying stimuli, including shear stress and both endogenous and exogenous vasodilators and vasoconstrictors. Estimates of vascular health are important clinically, as they are associated with adverse cardiovascular outcomes.[41] Furthermore, measurements of arterial compliance and endothelial reactivity are currently being used to assess CVD risk as they have been shown to predict future cardiovascular events.[42-44] The vascular adaptations to diabetes are multifactorial in nature and include changes to structure, dynamic characteristics (i.e. compliance and elastance) and cellular function (i.e. endothelial reactivity) of the artery.

2.2.1 *Vascular Morphology*

Vascular structure is typically assessed through echocardiographic determination of vessel wall thickness of large arteries. Carotid artery intima-media wall thickness (CIMT) has been shown to predict the development of atherosclerosis and is increased in various populations at risk for the development of CVD.[45] Furthermore, intima-medial wall thickness has been shown to be associated with the development of coronary artery disease[46] and may help identify asymptomatic individuals with underlying coronary artery disease.[47]

Several investigations have demonstrated that diabetes is associated with an increase in CIMT compared to age-matched non-diabetic controls.[48-50] Kawamori *et al.*[48] demonstrated that CIMT decreased with age, and that the regression coefficient for age was significantly greater in those with DM-2. Puija and colleagues[49] extended these findings by demonstrating that CIMT was greater in patients with DM-2 and that the enhanced CIMT was also associated with an approximate three-fold greater prevalence of atherosclerosis in this population.

In a large population-based sample, the Insulin Resistance Atherosclerosis Study assessed the relationship between metabolic variables associated with the insulin resistance syndrome (i.e. estimates of insulin sensitivity) and risk factors associated with the prevalence of CVD[51]. Insulin sensitivity was assessed using an oral glucose tolerance test as well as a frequently sampled intravenous glucose tolerance test. CIMT

was assessed using B-mode ultrasound and a number of hematological markers of CVD were measured in approximately 1600 men and women of varying ethnic backgrounds. The investigators reported a significant negative association between insulin sensitivity and CIMT in Hispanic and white non-hispanic patients, however this relationship was not evident in African-Americans.[52] The authors state that moderate differences in insulin sensitivity were associated with differences in CIMT similar in magnitude to those associated with many of the traditional cardiovascular risk factors. Thus, there appears to be a dose-response effect, such that for a given decline in insulin-mediated glucose uptake, there is a corresponding vascular hypertrophic response.

In a later study performed by the same group, the study sample was divided into those with and without DM-2. The authors confirmed that CIMT was significantly greater in DM-2, even after adjusting for co-existing risk factors for coronary heart disease.[53,54] Contrary to their initial findings, there were no differences in CIMT observed in persons with impaired glucose tolerance, suggesting that the increase in vessel wall thickness may be associated with the onset of the diabetic state.[53,54] More specifically, even though CIMT appears to be increased with the onset of DM-2, the duration of the disease was not associated with any further increase in wall thickness.[54] More recently, the authors have suggested that there is a heritability component to the increase in CIMT with DM-2.[55] Therefore, a genetic predisposition similar to that for the development of DM-2 itself, may contribute to arterial wall hypertrophy in this population.

In summary, although insulin resistance may or may not be coupled with alterations in CIMT, DM-2 is associated with vessel wall hypertrophy and there may be a genetic predisposition underlying this phenomenon. Furthermore, DM-2 is associated with an exaggerated age-related increase in CIMT, suggesting a distinct impact of the disease on arterial structure.

2.2.2 *Vascular Compliance*

Arterial compliance can be defined as the relationship between the changes in arterial dimension for a given change in the distending pressure.[56] Arterial compliance plays an important role in maintaining vascular hemodynamics as it controls resistance to

flow and therefore has an impact on LV loading conditions, as well as the stress/strain placed on the endothelial layer of the vessel walls.[57] There are several non-invasive methods for measuring arterial compliance or estimating vascular distensibility, which include the ratio of stroke volume to pulse pressure, changes in pulse wave velocity along the arterial tree, ultrasound estimates of pulsatility and pulse contour analysis of the arterial wave form.[58]

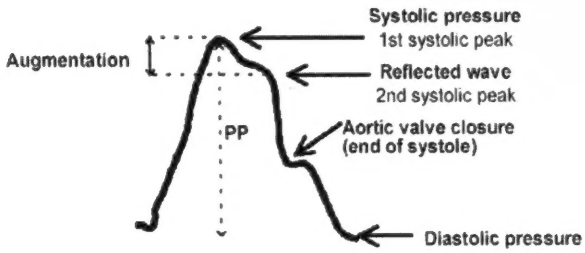
The increased incidence of CVD associated with changes in vascular structure is likely attributed to increased vessel stiffness or reductions in arterial compliance that accompany an increase in CIMT.[59] This has been demonstrated recently, as DM-2 was associated with increased aortic pulse wave velocity secondary to an increase in CIMT.[60,61] Taniwaki and colleagues[60] demonstrated a significant relationship between CIMT and aortic pulse wave velocity (a marker of arterial stiffening) in healthy controls and patients with DM-2. This relationship was stronger in DM-2, where both CIMT and aortic pulse wave velocity were significantly higher than their age-matched counterparts. It should be mentioned that there were significant differences in systolic blood pressure and cholesterol levels between groups. As these variables have been shown to be associated with increased CIMT and arterial stiffness, these findings should be interpreted with caution.

The association between increased intima-media wall thickness is not limited to central arteries, as similar findings have been demonstrated in large arteries of the lower limbs.[61] More importantly, the authors found that both femoral intima-media thickness and pulse velocity increased according to the number of co-existing features of the metabolic syndrome (i.e. increased waist-to-hip ratio, hypertension, hypercholesterolemia, low HDL). Therefore, the impact of each metabolic disorder associated with DM-2 may act independently on vascular structure and function, which may ultimately explain why the severity of the diabetic state is related to the risk for CVD.

The Windkessel model of arterial compliance is comprised of two elements, a capacitive element (large artery compliance) and an oscillatory element (small artery compliance), both of which can be assessed with invasive or non-invasive techniques (Figure 1).[62] It has been documented that DM-2 is associated with a significant decline

Figure 1. Graphical representation of tonometrically derived pressure wave form

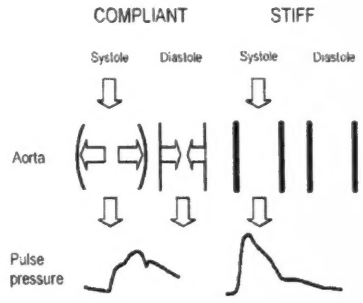
ARTERIAL STIFFNESS



in the oscillatory element of vascular compliance compared to non-diabetic controls without any changes in other hemodynamic variables (see Figure 2 for example).[8] A reduction in the oscillatory element of arterial compliance is also evident in type 1 diabetics with microvascular disease, suggesting that the duration of the disease or degree of metabolic control may contribute to altered vascular compliance.[63]

Conversely, McVeigh and colleagues[8] did not demonstrate differences in large artery stiffness between DM-2 and controls. However, aortic distensibility, assessed from doppler ultrasound-derived measurement of pulse wave velocity along the thoraco-abdominal aortic pathway has been found to be significantly reduced in patients with DM-2, compared to non-diabetic controls (74 ± 21 vs $100 \pm 18\%$).[64]

Figure 2. Graphical representation of increased arterial stiffness and subsequent changes in the peripheral arterial wave form



Paradoxically, patients with type 1 diabetes had a 48% greater aortic distensibility index than their age-matched controls suggesting that alterations specific to the state of DM-2 besides glucose tolerance may be responsible for the impaired vascular function.[64] This may be related to the effects of repeated exogenous insulin administration on vascular tone in individuals with type 1 diabetes.

The Atherosclerosis Risk in Communities study was a prospective investigation of the etiology and natural history of atherosclerosis in large communities in the United States.[65] Approximately 4700 men and women were investigated. Glucose tolerance and diagnosis of diabetes was determined from fasting glucose levels, history of diabetes or history of treatment with oral hypoglycemic agents. Several indexes of arterial stiffness were derived non-invasively from simultaneous measurements of arterial diameter (using B-mode ultrasound) and blood pressure determined automatically from the brachial artery. Type 2 diabetes was associated with stiffer arteries and metabolic parameters such as blood glucose and insulin levels displayed independent effects on arterial compliance secondary to the diseased state. More specifically, the authors reported that a 25% (1 standard deviation) increase in fasting blood glucose was associated with an approximate 6% decline in arterial compliance in men and a 15% decline in women with and without DM-2.

In conclusion, the reduced arterial distensibility associated with DM-2, concomitant to the increased CIMT are both considered risk factors for CVD.[66] Altered arterial compliance in DM-2 may therefore be a function of changes to vascular structure as previously discussed, but they may also be a function of a reduced vasodilatory reserve.

2.2.3 *Vascular Reactivity (Endothelial Function)*

A key regulator of vascular health is the endothelium-derived vasodilator nitric oxide.[67] Nitric oxide has been shown to protect against several events involved in atherosclerotic progression including: shear stress, platelet aggregation, monocyte adhesion, and oxidative stress.[68] In addition, increased arterial stiffness in DM-2 may reflect reduced nitric oxide bioavailability as nitric oxide has been shown to be responsible for regulating arterial compliance in human arteries.[56]

Estimation of nitric oxide bioavailability in humans is performed by measuring changes in arterial diameter in response to various stimuli,[69] such as acetylcholine, metacholine, bradykinin, insulin and shear stress following brief periods of ischemia (endothelial-dependent dilatation). Furthermore, the effectiveness of the nitric oxide signaling pathway on smooth muscle dilatation can be estimated by assessing the relative

change in arterial diameter in response to an exogenous nitrate donor (endothelial-independent dilatation).[41,70] Clinically, reduced endothelial-dependent dilatation is believed to be an antecedent to atherosclerosis and therefore changes associated with DM-2 may be marker of future macrovascular events in this population.

McVeigh *et al.*[8] found that patients with DM-2 had similar blood flow response to reactive hyperemia compared to healthy controls. However, the authors concluded that the diabetic state was associated with endothelial smooth muscle cell dysfunction, as the vasodilatory response to acetylcholine and exogenous nitrates were blunted in DM-2. Since then, several authors have supported these findings and have demonstrated impaired endothelial-dependent vasodilatation in response to intra-arterial acetylcholine infusion and shear stress in DM-2.[71-73]

The underlying mechanisms responsible for the attenuated endothelial-dependent dilatation appear to be metabolic in nature as endothelial dysfunction has been attributed to insulin resistance,[74, 75] hyperglycemia,[76], elevated cholesterol,[71,77] LDL particle size and/or oxidation,[78] the post prandial state[79] and is additive to the negative effects of hypertension on endothelial function.[80] Moreover, endothelial function has also been shown to improve secondary to improvements in insulin sensitivity[81-84] but not following lipid therapy.[85,87] Therefore, improved glycaemic control may be a realistic therapeutic target for endothelial dysfunction associated with DM-2.[87]

Although it appears that depressed nitric oxide-mediated vasodilatation may be responsible for the endothelial dysfunction in DM-2, it could also be a function of increased circulating levels of vasoconstricting paracrines such as endothelin-1.[88] Endothelin-1 acts on endothelin-A receptors on vascular smooth muscle and is the principle antagonist to nitric oxide. Increased circulating endothelin-1 levels,[89] endothelin-1 activity,[90] and sensitivity to endothelin-A antagonism[88,90,91] have been observed in DM-2. In support of the role of endothelin-1 in endothelial dysfunction in DM-2, resting and metacholine chloride-induced blood flow are normalized with endothelin-A receptor antagonism in obese and DM-2 individuals[91]. Moreover, inhibition of endothelin-1 significantly enhanced resting blood flow in DM-2, with little change observed in healthy controls.[90] Furthermore, Cardillo *et al.*[90] observed a blunted vasoconstrictory response to infused endothelin-1 in persons with DM-2, which is likely

a function of endothelin-A receptor down regulation following co-existing prolonged hyperendothelinemia and hyperinsulinemia.[92,93]

Regardless of the mechanism, there appears to be a reduction in endothelial-dependent dilatation in DM-2, which may contribute to the increased arterial stiffness observed in this population. More importantly, the reduced endothelial-dependent dilatation, increased arterial stiffness and increased CIMT observed in DM-2 are all associated with increased risk for CVD. Similar to the left ventricle, the vascular adaptation to DM-2 is characterized by a loss in arterial compliance. As previously mentioned, DM-2 is a disease that develops secondary to a sedentary lifestyle and reductions in vascular compliance may be more a reflection of the degree of sedentarism than the disease itself. It is therefore possible that increased levels of physical activity may attenuate arterial stiffening in DM-2 and reduce the risk for CVD.

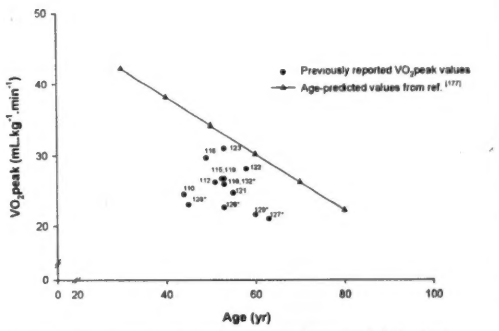
2.3 Cardiovascular Fitness in Type 2 Diabetes

The clinical implications of altered LV and vascular structure and function with DM-2 have been discussed, however the functional implications of these maladaptations are less well understood. LV and vascular function contribute significantly to cardiovascular fitness as they regulate oxygen delivery and blood flow distribution to exercising tissues. Therefore to assess coordinated cardiovascular function the most commonly accepted measurement is the maximal rate of oxygen consumption (VO_{2max}). VO_{2max} is a function of maximal heart rate and stroke volume as well as maximal peripheral oxygen extraction. VO_{2max} is measured clinically to quantify functional ability and in research settings to estimate the physical activity status and fitness levels of participants.

From a clinical standpoint, a low VO_{2max} is associated with an increased mortality in healthy persons, persons with a primary risk factor for CVD and those with DM-2.[94] On average, persons with DM-2 have VO_{2max} values that are 20-25% below that reported in age and gender-matched sedentary healthy individuals (Figures 3 & 4). Interestingly, epidemiological data suggest that high cardiorespiratory fitness in men with DM-2 is associated with better prognosis and may reduce the risk of CVD associated with the disease.[95] Thus reduced VO_{2max} in DM-2 is at least partly due to an excess fat mass in

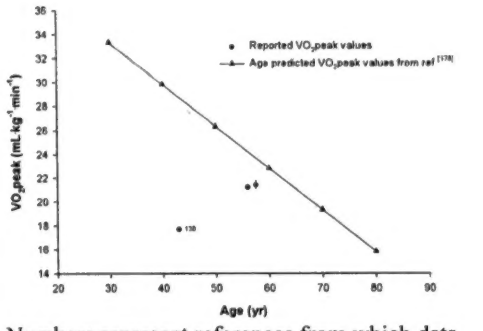
this population, but may also be a function of impaired LV or vascular function, as both have been shown to correlate with cardiorespiratory fitness.

Figure 3. VO_2max in men with DM-2



Numbers represent references from which data was obtained. Regression line was derived from Tanaka et al. [177]

Figure 4. VO_2max in women with DM-2



Numbers represent references from which data was obtained. Regression line was derived from Fitzgerald et al. [176]

2.3.1. *Cardiovascular Limitations to VO_{2max}*

In healthy individuals maximal cardiac output and oxygen supply to mitochondria have consistently been demonstrated to be the primary limitations to VO_{2max}.[96] It is likely that the same limitation will ultimately be the limiting factor in DM-2. However to date this has not been studied in this population. It is also of importance to describe which steps throughout the oxygen cascade are responsible for the reduced exercise capacity observed in DM-2 compared to age-matched healthy individuals. Unfortunately, very few studies have ever addressed which components of VO_{2max} are attenuated in DM-2 (i.e. cardiac output or a-vO_2 difference). Recently, cardiac output was measured non- invasively in 11 individuals with DM-2 and 12 non-diabetic controls during submaximal workloads and maximal data was extrapolated from these values.[97] Similar to previous reports (Figures 3 & 4) VO_{2max} was significantly lower in DM-2 (~26%) than sedentary, age and body composition matched controls. It would appear likely that this decrement was, in part, a function of the reduced cardiac output observed in the DM-2 (10.0 vs.11.2 l/min, respectively). However, this finding did not reach statistical significance. Interestingly, heart rate and not stroke volume was significantly lower at submaximal exercise intensities in DM-2.

With regards to oxygen delivery, blood flow distribution is second only to cardiac output in determining oxygen supply to the contracting skeletal muscle. A recent investigation performed by Kingwell and colleagues[98] compared the blood flow responses between persons with DM-2 and age-, sex-, VO_{2max} - and weight-matched non-diabetic peers. Blood flow was assessed using a thermodilution technique during cycling exercise at 60% of VO_{2max} and during graded doses of acetylcholine infusion. Two important findings from this investigation were that leg blood flow was impaired in response to both exercise and acetylcholine, and the blood flow response to either stimulus was significantly related to fasting plasma glucose levels. Although the authors did not measure blood flow distribution to working muscle, the data support the notion that control of peripheral blood flow during exercise is impaired in DM-2.

The sedentary lifestyles in this population may lead to a reduction in capillary density as well as a decrement in blood flow distribution. Paradoxically, Eriksson *et al.*[99] have demonstrated that DM-2 is associated with an increased capillary density and capillary to fiber ratio. However capillary recruitment or microvascular reactivity is blunted during exercise in DM-2.[100-102] Therefore, not only is blood flow response to exercise impaired in DM-2, but the ability to recruit capillaries within the exercising muscle is reduced as well.

2.3.2. *Peripheral Limitations to $\dot{V}O_{2max}$*

Arterio-venous oxygen difference is a function of the cardiovascular systems capacity to supply oxygen to the working muscles and the contracting muscle's ability to extract it. As with cardiac output and blood flow, relatively few studies have addressed whether oxygen extraction at peak exercise is attenuated in DM-2. In the aforementioned study by Baldi *et al.*[97] a significant decline in arterio-venous oxygen difference was observed in DM-2, which is likely due to an impairment in blood flow distribution, capillary density, capillary recruitment and/or mitochondrial density. However, it should be mentioned that arterio-venous oxygen difference was calculated using a non-invasive measurement of cardiac output that was extrapolated from submaximal values. Therefore these findings need to be substantiated by more invasive investigations.

A reduction in muscle mitochondrial density and function in DM-2,[103] may also explain the limited exercise capacity observed in this population. Mitochondrial

longitudinal area, aerobic enzyme (citrate synthase) activity and the functional capacity of the electron transport chain are all reduced in both insulin resistance and DM-2 when compared to lean healthy controls.[103-105] In addition, mitochondrial longitudinal area is correlated with insulin sensitivity suggesting that reduced mitochondrial function not only contributes to a decreased skeletal muscle oxidative reserve but may also explain the attenuated insulin sensitivity in this population.[103] As DM-2 is a disease associated with reduced levels of physical activity, the observations described above may be more a function of disuse than a distinct feature of DM-2. It is highly likely that similar to the left ventricular and vascular adaptation to DM-2, the peripheral maladaptation to DM-2 may be attenuated with increased levels of physical activity.

In summary, several sites along the oxygen transport cascade are impaired in DM-2. One, all or several of these sites may contribute to the reduced cardiorespiratory fitness observed in DM-2. Although there are several reports of cardiovascular and peripheral limitations to oxygen transport in this population, few investigators have attempted to design a study that specifically addresses the issue of limitations to maximal aerobic capacity in DM-2. Therefore, the major contributing factors associated with reduced functional capacity in DM-2 still need to be addressed.

3. Effects of Exercise Training on Cardiovascular Structure and Function in Type 2 diabetes

Current consensus statements that describe the role of exercise in the treatment of persons with DM-2 has focused on the benefits of exercise training on improving insulin sensitivity and/or glucose transport.[4,106-08] As previously stated, the morbidity and mortality associated with DM-2 are cardiovascular in origin and not a result of metabolic dysregulation. Although the cardioprotective effects of exercise in the aged are well documented, there is little data documenting the effects exercise training on cardiovascular function in persons with DM-2.[109] The remainder of this review will focus on the potentially beneficial effects of exercise training on cardiovascular function in DM-2.

3.1. Exercise Training and Cardiovascular Fitness

Cardiovascular fitness in DM-2 is increased following exercise training. Following a review of twenty-three investigations that have presently described the effects of aerobic-type exercise training on VO_{2max} in persons with DM-2, in which the authors have documented the frequency, duration, intensity and type of exercise performed (see Appendix Table 1) it was dertermined that the average improvement in VO_{2max} associated with aerobic exercise training is 13.2% (range 0-41%). The majority of these studies have prescribed exercise 3 times per week for durations ranging between 40 and 60 minutes, using exercises such as walking, jogging and stationary cycling.

To date few studies have described the effects of exercise training on cardiovascular parameters in DM-2. However, there is evidence to suggest that exercise may have therapeutic potential. Due to the paucity of available data presently in this area I have chosen to utilize a model of ageing, to support this hypothesis. I make this assumption as it is my contention that the cardiovascular adaptations, although worse in DM-2, are similar to those observed with the process of aging (i.e. reduced LV systolic reserve and LV filling subsequent to an increase in LV mass and wall thickness, with minimal change in resting LV systolic function).[133]

3.2. Left Ventricular Adaptations to Exercise Training

3.2.1 *Left Ventricular Structure*

With regards to LV morphology, aerobic exercise training is typically associated with the physiological increase in LV mass (i.e. the athletes heart), secondary to increased wall thickness and cavity dimension.[134] However, in DM-2 the goal of exercise training would be to regress LV concentric hypertrophy and decrease LV mass. A limited number of investigations have assessed the alterations in left ventricular morphology following exercise-mediated reductions in LV afterload in older populations with LV concentric hypertrophy.[135,136] Turner and colleagues[136] demonstrated that 7 months of endurance exercise training was associated with a significant regression of concentric hypertrophy, secondary to a decline in mean arterial pressure in a small sample (n=11) of older men with mild to moderate hypertension. Although the authors did not measure arterial compliance, re-analysis of their data would suggest that arterial elastance (estimated from the peak systolic blood pressure/stroke volume ratio) might be

decreased with exercise training, thereby reducing the arterial component of afterload and subsequently leading to a regressions of LV hypertrophy. In support of these findings, Kokkinos *et al.*[135] reported that 16 weeks of exercise in addition to antihypertensive therapy elicited a 14% decline in LV mass indexed for body weight secondary to 8 and 6% reductions in interventricular and posterior wall thickness, respectively, with little change in cavity area. In addition, decreases of approximately 10% in LV wall mass with exercise training have also been reported in middle-aged hypertensive populations.[137-139] From these studies in populations with LV concentric hypertrophy similar to that observed in DM-2, it is possible that exercise training could significantly reduce LV mass and wall thickness in persons with DM-2.

3.2.2 *Left Ventricular Function*

Improvements in VO_{2max} following exercise training in DM-2 may be a function of enhanced LV diastolic filling, as it is highly correlated with cardiorespiratory fitness in other populations.[34,35] Similarly, if exercise training has been shown to regress LV concentric hypertrophy, one would expect a concomitant improvement in diastolic filling and possibly VO_{2max}.[140] However, early to late diastolic filling velocities have been shown to be unaltered subsequent to favorable changes to LV morphology following exercise training.[136] Despite the finding of Turner *et al.*[136] there is substantial data to support the role of exercise training in the treatment of impaired LV filling dynamics associated with age or DM-2.

Left ventricular diastolic filling has been shown to correlate well with VO_{2max} in healthy young adults,[34] older healthy adults[141] patients with longstanding hypertension [27] and men with DM-2.[23] Furthermore, age-associated reductions in LV filling appear to be attenuated in master's athletes who perform vigorous endurance training 5-7 days per week.[142-145] Specifically, Douglas and O'Toole[143] have demonstrated that the ratio of early to late diastolic transmitral flow velocity is elevated in athletes of any age, when compared to their sedentary age-matched counterparts. Similarly, endurance training has been shown to enhance early diastolic filling at rest and during exercise in older previously sedentary men.[145-147] It is therefore possible that LV filling abnormalities associated with DM-2 may be attenuated in a similar fashion, with exercise training.

Despite limited data in this area, Poirier *et al.*[23] have demonstrated that impaired LV filling dynamics were associated with significant reductions in exercise capacity in men with DM-2.

Improvements in cardiorespiratory fitness observed following exercise training might also be mediated through enhanced LV systolic function or blood flow distribution. The problem with identifying the mechanisms that improve VO_{2max} following exercise training in older populations is that few studies have measured LV performance and blood flow distribution simultaneously during exercise. Exercise training elicits enhanced LV contractile reserve in older men free from cardiovascular disease evidenced by a steeper slope of the fractional shortening-end-systolic wall stress relationship, established following β-adrenergic stimulation[146-148]. Although these findings suggest enhanced contractile reserve following exercise training, the authors did not assess LV function at maximal exercise intensities. Interestingly, enhanced LV β-adrenergic sensitivity was not observed in older women following exercise training suggesting that improvements in cardiovascular fitness following exercise training in older women might be related to changes in blood flow distribution and oxygen utilization and less a function of changes in LV function.[149] Exercise training is also associated with changes in mitochondrial density and function, which would also explain increased VO_{2max} following exercise training in older women. In support of this, improvements in VO_{2max} in older men following short-term endurance training have been attributed to heightened peripheral circulatory changes, such as improved blood flow distribution with little change in cardiac output.[150]

In summary, exercise training has been shown to attenuate age-related changes in LV morphology, diastolic filling and systolic reserve, all of which are adversely altered in DM-2. If LV filling dynamics can serve as a crude estimate of LV compliance, it would appear that exercise may be beneficial in attenuating the reductions in LV compliance observed in DM-2.

3.3. Vascular Adaptations to Exercise Training

Several lines of evidence suggest that increased levels of physical activity are associated with a favorable improvement in vascular health. Firstly, vascular compliance and endothelial-dependent dilatation are associated with a higher VO_{2max} in healthy older individuals.[151-154] Secondly, large population based samples have demonstrated that age-related declines in arterial compliance and endothelial-dependent dilatation may be attenuated with increased physical activity patterns in both men and women.[155-159] Finally, data from interventional studies suggest that short term (12-16 weeks) exercise training elicits favorable changes in arterial compliance and endothelial-dependent dilatation with age [158] and DM-2.[160] Therefore, there appears to be ample evidence to infer that exercise may be beneficial in the treatment of the vascular disorders associated with DM-2.

3.3.1 *Vascular Structure*

Data from the Atherosclerosis Risk in Communities study demonstrated that CIMT increased with body mass index, metabolic control and waist to hip ratio.[161] More importantly, CIMT was also found to be lower in all groups of patients, including those with DM-2, in the highest quartile of physical activity score. These data imply that those who perform the highest amount of physical activity display the lowest CIMT, regardless of co-existing risk factors for CVD. This observation is supported by recent data that demonstrated a small but significant positive correlation between vascular structure and cardiovascular fitness in older patients with long standing hypertension.[162]

Recently, Tanaka *et al.*[163] examined the role of physical activity on the age-related increase in CIMT in men. The participants were stratified into three groups based on age (young [18-37 yr], middle aged [38-57], and older [58-77]). CIMT and carotid arterial blood pressure increased significantly with age in both the sedentary and physically active groups. However, there were no differences in vascular structure between the physically active older men and their sedentary younger peers. The beneficial effects of physical activity on vascular structure have also been demonstrated in women, as those who performed regular physical activity displayed lower femoral intima-medial thickness.[164] Interestingly, the reductions in intima-medial thickness were site specific, such that both brachial and carotid intima-medial thickness did not change

in relation to physical activity status. The effects of physical activity levels on intima-medial thickness is not uniform however as Schmidt-Truckass *et al.*[165] observed a significant relationship between physical activity status and arterial compliance as well as significant differences between groups of high and low physical activity status, despite no change in vascular structure.

In the majority of the aforementioned cross sectional investigations, an exercise intervention was included to determine the effects of a 16-week home-based exercise training program on estimates of arterial compliance. Following these interventions small changes in central arterial compliance were observed in men[157], however, no change was observed in CIMT.[163] The training stimulus in these studies is questionable as they report minimal changes in cardiorespiratory fitness following training. However, peripheral arterial remodeling (increased lumen diameter and decreased wall thickness) following equivalent training regimes have been documented in other studies with middle aged men.[166] Although the available literature suggests a reduced vascular wall thickness with increased levels of exercise in persons with age-related increases in vascular morphology, we are currently unaware of any investigations, which have addressed the issue of the effects of an exercise training intervention on vascular morphology in persons with DM-2.

In summary, there does appear to be an association between vascular structure and physical activity status. This has been shown using cross sectional data, linear regression models and interventional studies. Moreover the majority of investigations that have shown improved arterial compliance with increased levels of physical activity have reported changes in vascular structure to explain their findings.

3.3.2 *Vascular Compliance*

The role of enhanced levels of physical activity on arterial compliance was examined by the Baltimore Longitudinal Study of Aging who investigated the relationship between VO_{2max} and aortic pulse wave velocity in 146 men and women 21-90 years of age.[155] The authors suggest that exercise may attenuate the age-related decline in arterial stiffness as the age-related reduction in arterial compliance was less dramatic in masters endurance athletes, compared to their sedentary peers. Tanaka *et*

al.[156] demonstrated that physical activity eliminated age-related differences in aortic pulse wave velocity and augmentation index observed in sedentary females. Similar to the observations made by Vaitkevicius and colleagues[155] a significant negative relationship ($r = -0.66$, $p < 0.005$) was found between central arterial stiffness and VO_{2max}. Similar relationships between VO_{2max} and arterial compliance have also been reported elsewhere, as arterial compliance in endurance-trained middle-aged and older men was 20% to 35% higher than their less active peers.[157]. Furthermore, large artery reserve, assessed from a tonometrically derived wave form on the carotid artery, has been shown to correlate with VO_{2max} ($r = 0.34$, $p<0.03$) in healthy, older men and women.[152] Although relationships and cross sectional data do not represent cause and effect, they do provide evidence to support the role of exercise in the reduction of age-related increases in arterial stiffness. Tanaka *et al.*[156] did observe a 25% improvement in arterial compliance with an ~20% reduction in arterial stiffness following a home based 16-week aerobic exercise training intervention in a sub-sample of men studied. However, similar findings were not observed in an older group of men and women with isolated systolic hypertension.[167] This discrepancy may be due to the lower exercise training intensities employed by these authors. In support of this observation, cross sectional investigations have demonstrated that the age-related declines in arterial compliance may be attenuated with high-intensity exercise training, but not with low-intensity recreational-type physical activity.[157]

3.3.3. *Vascular Reactivity (Endothelial Function)*

There is ample evidence to suggest that exercise training may be beneficial in attenuating reductions in endothelial function in several populations. Firstly, there is a moderate linear relationship ($r=0.66$, $p<0.002$) between endothelial-dependent dilatation and VO_{2max} in older men.[154] In the same study the authors also report that endothelial reactivity to shear stress was enhanced in master's athletes (68.5 ± 2.3 yrs) as their 64% higher VO_{2max} was coupled with a significantly greater ratio of endothelial-dependent/independent dilatation. Secondly, cross sectional data have shown that aerobic training prevents and restores age-related declines in endothelial-dependent vasodilation in healthy older men.[158]. Specifically, forearm blood flow responses to graded doses of

acetylcholine and sodium nitroprusside were measured using strain-gauge plethysmography. Young and older endurance trained men demonstrated similar changes in forearm blood flow in response to acetylcholine, suggesting a more sensitive endothelial layer. Rywik *et al.*[153] support this work as they demonstrated an improvement in endothelial-dependent dilatation in response to reactive hyperemia in endurance trained older men compared to their sedentary counterparts. Finally, an enhanced blood flow response to exercise and greater arterial dilatory reserve has been demonstrated in older endurance trained men compared to their sedentary peers.[168] All of these findings are relevant as enhanced vascular reactivity with exercise training may be an adaptation that allows for greater muscle perfusion during exercise, and thereby allows for increased rates of oxidative phosphorylation. As DM-2 is also associated with a reduction in endothelial-dependent dilatation, it is possible that similar improvements with exercise training may be obtained in persons with DM-2.

Data from intervention studies support cross sectional studies as exercise training has also been shown to improve peripheral or coronary endothelial-dependent dilatation in patients with insulin resistance,[160,169] hypertension,[170] and heart failure.[171-174] More specifically to the topic of this review, in patients with metabolic syndrome, flow mediated (i.e. endothelial-dependent) dilatation increased from 5.3 ± 2.8% to 7.3 ±2.7% without any change in body mass index, blood pressure or insulin sensitivity following 12 weeks of exercise training.[169] More recently, in a small mixed cohort of patients with type 2 diabetes, as little as eight weeks of exercise training has been shown to increase flow-mediated dilatation as much as 3-fold.[174] Sixteen patients with type 2 diabetes (52 ± 2 yrs) participated in an interventional cross over design where eight weeks of training was followed by eight weeks of detraining. Endothelial function was assessed invasively with strain gauge plethysmography in response to graded doses of acetylcholine and sodium nitroprusside and non-invasively with flow mediated dilatation. Exercise training consisted of three one-hour sessions per week, of both aerobic and resistance exercise performed at 75-85% of heart rate reserve and 55-65% of maximal voluntary contraction respectively. Exercise training elicited reductions in fasting glucose, HbA_{1C} and heart rate, with no change in lipid profile. Although flow-mediated dilatation increased nearly three-fold following training, the increase in blood flow in response to acetylcholine and

sodium nitroprusside was not as striking (21 and 23% at maximal doses respectively). As the authors combined the data into trained and untrained states, the effects of detraining were difficult to decipher, however they suggest that exercise-mediated improvements in vascular function are not persistent and likely regress rapidly with detraining.[174]

3.4. Summary

The observation that exercise may enhance arterial compliance, vascular structure and endothelial-dependent dilatation, are clinically relevant, as all of these assessments of vascular health are associated with CVD morbidity and mortality. Therefore, increased levels of physical activity may be used therapeutically to attenuate the significant risk of CVD mortality associated with the disease. Functionally, increased levels of physical activity may also be used to attenuate the significant reduction in functional reserve associated with the DM-2, which could subsequently improve the quality of life in these patients as has previously been demonstrated in other populations.

The incidence of type 2 diabetes is increasing at an alarming rate in western societies likely from a reduction in physical activity.[175,176] As type 2 diabetes is associated with a 3-5 fold increase in CVD mortality and morbidity, therapeutic interventions in this population need to have cardiovascular, as well as metabolic consequences. The increased incidence of CVD in this population appears to be linked to alterations in cardiovascular structure and function that ultimately present as a reduction in both left ventricular and vascular compliance. These adverse adaptations to the diabetic state likely contribute to the reduced cardiovascular fitness observed in this population. As significant information exists to demonstrate the therapeutic potential of exercise in populations with similar decrements in cardiovascular function, it is our belief that exercise has similar potential in the type 2 diabetic cardiovascular system. For this reason, physical activity may prove to be the ideal intervention in DM-2 as not only does it have the potential to reduce CVD incidence but it has been shown to minimize unwanted cardiovascular adaptations in other diseased populations, but also the favorable effects on glucose metabolism.

4. Conclusions

In conclusion, I contend that cardiovascular complications associated with DM-2 are essentially a problem of compliance, as it stems from a lack of compliance to physical activity and is characterized by a non-compliant cardiovascular system. The three in concert likely explain the increased incidence of CVD mortality and morbidity in this population. By improving compliance to physical activity it is possible that the incidence of CVD in this population may be greatly reduced.

5. Aims and Hypotheses

Upon review of the literature the following hypotheses and specific aims have been developed:

Study 1

Hypothesis 1 - Exercise training, regardless of the type will increase VO_{2peak} in older women, secondary to an increase in LV filling dynamics.

Hypothesis 2 - The impact of strength training on VO_{2peak} and LV filling dynamics will be equal to and additive to that observed with aerobic training.

Specific aims: Determine the independent and additive effects of aerobic and strength training on LV structure and function in healthy post menopausal women.

Study 2

Hypothesis - Exercise training will enhance arterial compliance and LV filling dynamics secondary to an improvement in VO_{2peak} in women with DM-2.

Specific aims - To assess the cardiovascular adaptations to exercise training in women with DM-2.

Study 3

Hypothesis - Exercise training will increase arterial compliance secondary to an improvement in endothelial-dependent dilatation in women with DM-2.

Specific aims – To assess the vascular adaptations to exercise training in women with DM-2.

Study 4

Hypothesis - Low cardiorespiratory fitness will be associated with a decline in arterial compliance and LV filling dynamics in women with DM-2, despite no differences in conventional markers of CVD.

Specific aim - To examine novel and conventional risk factors in women with DM-2 stratified according to cardiorespiratory fitness.

REFERENCES

1. Celsus AC, De medicina (Spencer WG, trans). London: William Heinmann; Cambridge and Massachusetts: Harvard University Press, 1935; Vol. I ; Book IV 27.1 E-28.2.

2. Joslin EP, Root HF, White P et al. The treatment of Diabetes Mellitus. 1935. Philadelphia, PA: Lea Febiger.

3. Tuomilehto J, Lindstrom J, Eriksson JG et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344:1343-50.

4. American College of Sports Medicine and American Diabetes Association joint position statement. Diabetes mellitus and exercise. Med Sci Sports Exerc. 1997, 29:i-vi.

5. Haffner SM, Lehto S, Ronnemma T et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. N Engl J Med 1998, 339:229–234.

6. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241:2035-8.

7. Devereux RB, Roman MJ, Paranicas M et al. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation. 2000;101:2271-6.

8. McVeigh G, Brennan G, Hayes R et al. Vascular abnormalities in non-insulin-dependent diabetes mellitus identified by arterial waveform analysis. Am J Med. 1993;95:424-30.

9. Fletcher GF, Balady G, Blair SN, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1996;94:857-62.

10. Factor SM, Minase T, Sonnenblick EM. Clinical and morphologic features of human hypertensive diabetic cardiomyopathy. Am Heart J. 1980;99:446–458.

11. Fein FS, Sonnenblick EH. Diabetic cardiomyopathy. Prog Cardiovasc Dis. 1985; 27:255-70.

12. Taegtmeyer H, McNulty P, Young ME: Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation. 2002;105:1727-33.

13. Galderisi M, Anderson KM, Wilson PWF, et al. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy: the Framingham Heart Study. Am J Cardiol. 1991;68:85–89.

14. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34:29-34.

15. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561–1566.

16. Barrett-Connor EL, Cohn BA, Wingard DL et al. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991;265:627-31.

17. Fang ZY, Yuda S, Anderson V et al. Echocardiographic detection of early diabetic myocardial disease. J Am Coll Cardiol. 2003;41:611-7.

18. de Simone G, Devereux RB, Roman MJ, et al. Assessment of left ventricular function by the mid-wall fractional shortening-end-systolic stress relation in human hypertension. J Am Coll Cardiol. 1994;23:1444–1451.

19. Hsu KL, Chiang FT, Lo HM et al. Cardiac contractility in noninsulin dependent diabetes mellitus evaluated using the relation between endsystolic wall stress and velocity of circumferential fiber shortening. Jpn Heart J. 1997;38:463-71.

20. Sasso FC, Carbonara O, Cozzolino D et al. Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. J Am Coll Cardiol. 2000;36:219-26.

21. Takahashi N, Iwasaka T, Sugiura T et al.. Left ventricular dysfunction during dynamic exercise in noninsulin-dependent diabetic patients with retinopathy. Cardiology. 1991;78:23-30.

22. Poirier P, Bogaty P, Garneau C et al. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care. 2001;24:5-10.

23. Poirier P, C Garneau P, Bogaty P et al. Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol. 2000; 85:473-7.

24. Liu JE, Palmieri V, Roman MJ et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol. 2001;37:1943-9.

25. Zabalgoitia M, Ismaeil MF, Anderson L, et al. Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol. 2001; 87:320-3.

26. Bella JN, Palmieri V, Roman MJ et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation. 2002;105:1928-33.

27. Gerdts E, Bjornstad H, Toft S et al. Impact of diastolic doppler indices on exercise capacity in hypertensive patients with electrocardiographic left ventricular hypertrophy (a LIFE substudy). J Hypertens. 2002;20:1223-9.

28. Aronson D. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. J Hypertens. 2003;21:3-12.

29. Alpert MA, Lambert CR, Terry BE et al. Influence of left ventricular mass on left ventricular diastolic filling in normotensive morbid obesity. Am Heart J. 1995;130:1068-73.

30. Alpert MA, Terry BE, Mulekar M et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol. 1997;80:736-40.

31. Mureddu GF, de Simone G, Greco R et al. Left ventricular filling pattern in uncomplicated obesity. Am J Cardiol. 1996;77:509-14.

32. Nagano N, Nagano M, Yo Y et al. Role of glucose intolerance in cardiac diastolic function in essential hypertension. Hypertension. 1994; 23:1002-5.

33. Seto S, Kapuku GK, Kawahara , et al. Influence of mild to moderate obesity on left ventricular stress filling pattern in hypertension. Hypertens Res. 1998;21:245-50.

34. Vanoverschelde JJ, Essamri B, Vanbutsele R et al. Contribution of left ventricular diastolic function to exercise capacity in normal subjects. J Appl Physiol. 1993; 74:2225-33.

35. Lapu-Bula R, Robert A, De Kock M et al. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 1999;83:728-34.

36. Sakate Y, Yoshiyama M, Hirata K et al. Relationship between doppler-derived left ventricular diastolic function and exercise capacity in patients with myocardial infarction. Jpn Circ J. 2001; 65:627-31.

37. Kitzman DW, Higginbotham MB, Cobb FR et al. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. 1991;17:1065-72.

38. Danielsen R, Nordrehaug JE, Vik-Mo H. Left ventricular performance during exercise in long-term type 1 diabetic men: an echocardiographic study. Clin Physiol. 1988; 8:475-86.

39. Borow KM, Jaspan JB, Williams KA et al. Myocardial mechanics in young adult patients with diabetes mellitus: effects of altered load, inotropic state and dynamic exercise. J Am Coll Cardiol. 1990;15:1508-17.

40. Levine et al, MSSE(2003) abstract

41. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med. 1999;340:115–126.

42. Arnett DK, Evans GW, Riley WA: Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol. 1994; 140:669–682.

43. Hodes RJ, Lakatta EG, McNeil CT. Another modifiable risk factor for cardiovascular disease? some evidence points to arterial stiffness. J Am Geriatr Soc. 1995; 43:581–582.

44. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000; 101: 1899–1906.

45. O'Leary DH, Polak JF, Kronmal RA et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999;340:14-22.

46. O'Leary DH, Polak JF, Kronmal RA et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. Stroke. 1992;23:1752–1760.

47. Nagai Y, Metter EJ, Earley CJ et al. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. Circulation. 1998;98:1504-9.

48. Kawamori R, Yamasaki Y, Matsushima H et al. Prevalence of carotid atherosclerosis in diabetic patients: ultrasound high-resolution B-mode imaging on carotid arteries. Diabetes Care. 1992;15:1290-1294.

49. Pujia A, Gnasso A, Irace C et al. Common carotid arterial wall thickness in NIDDM subjects. Diabetes Care. 1994;17:1330-1336.

50. Niskanen L, Rauramaa R, Miettinen H et al. Carotid artery intima-media thickness in elderly patients with NIDDM and in nondiabetic subjects. Stroke. 1996;27:1986-1992.

51. Wagenknecht LE, Mayer EJ, Rewers M et al. The insulin resistance atherosclerosis study (IRAS) objectives, design, and recruitment results. Ann Epidemiol. 1995;5:464-72.

52. Howard G, O'Leary DH, Zaccaro D et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation. 1996;93:1809-17.

53. Wagenknecht LE, D'Agostino R Jr, Savage PJ et al. Duration of diabetes and carotid wall thickness. The Insulin Resistance Atherosclerosis Study (IRAS). Stroke. 1997;28:999-1005.

54. Wagenknecht LE, D'Agostino RB Jr, Haffner SM, et al. Impaired glucose tolerance, type 2 diabetes, and carotid wall thickness: the Insulin Resistance Atherosclerosis Study. Diabetes Care. 1998;21:1812-8.

55. Lange LA, Bowden DW, Langefeld CD et al. Heritability of carotid artery intima-medial thickness in type 2 diabetes. Stroke. 2002;33:1876-81.

56. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, Ganz P. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. Hypertension. 2001;38:1049-53.

57. O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. Hypertension. 1990;15:339-47.

58. Cameron JD, Gatzka CD, Kingwell BA. Assessment of large artery function. Coron Artery Dis. 2002;13:405-13.

59. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation. 2003;107:139-46

60. Taniwaki H, Kawagishi T, Emoto M et al. Correlation between the intima-media thickness of the carotid artery and aorticpulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. Diabetes Care. 1999;22:1851-7.

61. O'Neal DN, Dragicevic G, Rowley KG et al. A cross-sectional study of the effects of type 2 diabetes and other cardiovascular risk factors on structure and function of nonstenotic arteries of the lower limb. Diabetes Care. 2003;26:199-205.

62. Cohn JN. Arterial compliance to stratify cardiovascular risk: more precision in therapeutic decision making. Am J Hypertens. 2001;14:258S-263S.

63. Romney JS, Lewanczuk RZ. Vascular compliance is reduced in the early stages of type 1 diabetes. Diabetes Care. 2001;24:2102-6.

64. Lehmann ED, Gosling RG, Sonksen PH. Arterial wall compliance in diabetes. Diabet Med. 1992;9:114-9.

65. Salomaa V, Riley W, Kark JD, et al. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation. 1995;91:1432-43.

66. Simons PC, Algra A, Bots ML et al. Common Carotid Intima-Media Thickness and Arterial Stiffness: Indicators of Cardiovascular Risk in High-Risk PatientsThe SMART Study (Second Manifestations of ARTerial disease) Circulation. 1999;100:951 – 957.

67. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med. 1993;329:2002-12.

68. Gewaltig MT, Kojda G. Vasoprotection by nitric oxide: mechanisms and therapeutic potential. Cardiovasc Res. 2002;55:250-60.

69. Celermajer DS, Sorensen KE, Gooch VM et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340:1111-5.

70. Celermajer DS. Endothelial dysfunction: does it matter? Is it reversible? J Am Coll Cardiol. 1997;30:325-33

71. Watts GF, O'Brien SF, Silvester W et al. Impaired endothelium-dependent and independent dilatation of forearm resistance arteries in men with diet-treated non-insulin-dependent diabetes: role of dyslipidaemia. Clin Sci (Lond). 1996;91:567-73.

72. Williams SB, Cusco JA, Roddy MA et al. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J Am Coll Cardiol. 1996;27:567-74.

73. Hogikyan RV, Galecki AT, Pitt B et al. Specific impairment of endothelium-dependent vasodilation in subjects with type 2 diabetes independent of obesity. J Clin Endocrinol Metab. 1998;83:1946-52.

74. Steinberg HO, Chaker H, Leaming R et al. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest. 1996;97:2601-10.

75. Balletshofer BM, Rittig K, Enderle MD et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. Circulation. 2000;101:1780-4.

76. Title, LM, Cummings PM, Giddens K et al. Oral glucose loading acutely attenuates endothelium-dependent vasodilation in healthy adults without diabetes: an effect prevented by vitamins C and E. J Am Coll Cardiol. 2000;36:2185-2191.

77. McNeill KL, Fontana L, Russell-Jones DL et al. Inhibitory effects of low-density lipoproteins from men with type II diabetes on endothelium-dependent relaxation. J Am Coll Cardiol. 2000;35:1622-7.

78. Makimattila S, Liu ML, Vakkilainen J et al. Impaired endothelium-dependent vasodilation in type 2 diabetes. Relation to LDL size, oxidized LDL, and antioxidants. Diabetes Care. 1999;22:973-81.

79. Shige H, Ishikawa T, Suzukawa M et al. Endothelium-dependent flow-mediated vasodilation in the postprandial state in type 2 diabetes mellitus. Am J Cardiol. 1999;84:1272-4, A9.

80. Preik M, Kelm M, Rosen P et al. Additive effect of coexistent type 2 diabetes and arterial hypertension on endothelial dysfunction in resistance arteries of human forearm vasculature. Angiology. 2000;51:545-54.

81. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37:1344-50.

82. Rask-Madsen C, Ihlemann N et al. Insulin therapy improves insulin-stimulated endothelial function in patients with type 2 diabetes and ischemic heart disease. Diabetes. 2001;50:2611-8.

83. Gaenzer H, Neumayr G, Marschang P et al. Effect of insulin therapy on endothelium-dependent dilation in type 2 diabetes mellitus. Am J Cardiol. 2002;89:431-4.

84. Caballero AE, Saouaf R, Lim SC et al. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. Metabolism. 2003;52:173-80.

85. van de Ree MA, Huisman MV, de Man FH et al. Impaired endothelium-dependent vasodilation in type 2 diabetes mellitus and the lack of effect of simvastatin. Cardiovasc Res. 2001;52:299-305.

86. van Etten RW, de Koning EJ, Honing ML et al. Intensive lipid lowering by statin therapy does not improve vasoreactivity in patients with type 2 diabetes. Arterioscler Thromb Vasc Biol. 2002;22:799-804.

87. Bagg W, Whalley GA, Gamble G, Drury PL, Sharpe N, Braatvedt GD. Effects of improved glycaemic control on endothelial function in patients with type 2 diabetes. Intern Med J. 2001;31:322-8.

88. Mather KJ, Mirzamohammadi B, Lteif A et al. Endothelin contributes to basal vascular tone and endothelial dysfunction in human obesity and type 2 diabetes. Diabetes. 2002;51:3517-23.

89. Morise T, Takeuchi Y, Kawano M et al. Increased plasma levels of immunoreactive endothelin and von Willebrand factor in NIDDM patients. Diabetes Care. 1995;18:87 –89.

90. Cardillo C, Campia U, Bryant MB, et al. Increased activity of endogenous endothelin in patients with type II diabetes mellitus. Circulation. 2002;106:1783-7.

91. McAuley DF, McGurk C, Nugent AG, et al. Vasoconstriction to endothelin-1 is blunted in non-insulin-dependent diabetes: a dose-response study. J Cardiovasc Pharmacol. 2000; 36: 203–208.

92. Oliver FJ, de la Rubia G, Feener EP, et al. Stimulation of endothelin-1 gene expression by insulin in endothelial cells. J Biol Chem. 1991;266:23251–23256.

93. Ferri C, Pittoni V, Piccoli A, et al. Insulin stimulates endothelin-1 secretion from human endothelial cells and modulates its circulating levels in vivo. J Clin Endocrinol Metab. 1995;80:829–835.

94. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.

95. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 2000;132:605-11.

96. Richardson RS. What governs skeletal muscle VO2max? New evidence. Med Sci Sports Exerc. 2000;32:100-7.

97. Baldi JC, Aoina JL, Oxenham HC et al. Reduced exercise arteriovenous O2 difference in Type 2 diabetes. J Appl Physiol. 2003;94:1033-8.

98. Kingwell BA, Formosa M, Muhlmann M et al. Type 2 Diabetic Individuals Have Impaired Leg Blood Flow Responses to Exercise: Role of endothelium-dependent vasodilation. Diabetes Care. 2003;26:899-904.

99. Eriksson KF, Saltin B, Lindgarde F. Increased skeletal muscle capillary density precedes diabetes development in men with impaired glucose tolerance. A 15-year follow-up. Diabetes. 1994;43:805-8.

100. Katz MA, McNeill G. Defective vasodilation response to exercise in cutaneous precapillary vessels in diabetic humans. Diabetes. 1987;36:1386-96.

101. Katz MA, McCuskey P, Beggs JL et al. Relationships between microvascular function and capillary structure in diabetic and nondiabetic human skin. Diabetes. 1989;38:1245-50.

102. Menon RK, Grace AA, Burgoyne W et al. Muscle blood flow in diabetes mellitus. Evidence of abnormality after exercise. Diabetes Care. 1992;15:693-5.

103. Kelley DE, He J, Menshikova EV et al. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. Diabetes. 2002; 51:2944-50.

104. Vodra K, Rath R, Bass A et al. Enzyme activities in quadriceps femoris muscle of obese diabetic male patients. Diabetologia. 1977; 13:527 –529.

105. Lithell H, Lindgarde F, Hellsing K et al. Body weight, skeletal muscle morphology, and enzyme activities in relation to fasting serum insulin concentrations and glucose tolerance in 48-year-old men. Diabetes. 1977; 30:19 – 25.

106. Clark CM Jr, Lee DA. Prevention and treatment of the complications of diabetes mellitus. N Engl J Med. 1995;332:1210-7.

107. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med. 1998;49:235-61.

108. Ivy JL, Zderic TW, Fogt DL. Prevention and treatment of non-insulin-dependent diabetes mellitus. Exerc Sport Sci Rev. 1999; 27:1-35.

109. Ruderman NB, Schneider SH. Diabetes, exercise, and atherosclerosis. Diabetes Care. 1992; 15:1787-93.

110. Ruderman NB, Ganda OP, Johansen K. The effect of physical training on glucose tolerance and plasma lipids in maturity-onset diabetes. Diabetes. 1979; 28 Suppl 1:89-92.

111. Bogardus C, Ravussin E, Robbins DC et al. Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. Diabetes. 1984;33:311-8.

112. Schneider SH, Amorosa LF, Khachadurian AK et al. Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1984;26:355-60.

113. Trovati M, Carta Q, Cavalot F et al. Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. Diabetes Care. 1984;7:416-20.

114. Reitman JS, Vasquez B, Klimes I et al. Improvement of glucose homeostasis after exercise training in non-insulin-dependent diabetes. Diabetes Care. 1984;7:434-41.

115. Ronnemaa T, Mattila K, Lehtonen A et al. A controlled randomized study on the effect of long-term physical exercise on the metabolic control in type 2 diabetic patients. Acta Med Scand. 1986;220:219-24.

116. Lampman RM, Schteingart DE, Santinga JT et al. The influence of physical training on glucose tolerance, insulin sensitivity, and lipid and lipoprotein concentrations in middle-aged hypertriglyceridaemic, carbohydrate intolerant men. Diabetologia. 1987;30:380-5.

117. Skarfors ET, Wegener TA, Lithell H et al. Physical training as treatment for type 2 (non-insulin-dependent) diabetes in elderly men. A feasibility study over 2 years. Diabetologia. 1987;30:930-3.

118. Rogers MA, Yamamoto C, King DS et al. Improvement in glucose tolerance after 1 wk of exercise in patients with mild NIDDM. Diabetes Care. 1988;11:613-8.

119. Ronnemaa T, Marniemi J, Puukka P et al. Effects of long-term physical exercise on serum lipids, lipoproteins and lipid metabolizing enzymes in type 2 (non-insulin-dependent) diabetic patients. Diabetes Res. 1988;7:79-84.

120. Segal KR, Edano A, Abalos A et al. Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. J Appl Physiol. 1991;71:2402-11.

121. Schneider SH, Khachadurian AK, Amorosa LF et al. Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care. 1992;15:1800-10.

122. Dela F, Ploug T, Handberg A et al. Physical training increases muscle GLUT4 protein and mRNA in patients with NIDDM. Diabetes. 1994;43:862-5.

123. Smutok MA, Reece C, Kokkinos PF et al. Effects of exercise training modality on glucose tolerance in men with abnormal glucose regulation. Int J Sports Med. 1994;15:283-9.

124. Lehmann R, Vokac A, Niedermann K et al. Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. Diabetologia. 1995;38:1313-9.

125. Poirier P, Catellier C, Tremblay A et al. Role of body fat loss in the exercise-induced improvement of the plasma lipid profile in non-insulin-dependent diabetes mellitus. Metabolism. 1996;45:1383-7

126. Dunstan DW, Mori TA, Puddey IB et al. The independent and combined effects of aerobic exercise and dietary fish intake on serum lipids and glycemic control in NIDDM. A randomized controlled study. Diabetes Care. 1997;20:913-21.

127. Ligtenberg PC, Hoekstra JB, Bol E, et al. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. Clin Sci (Lond). 1997;93:127-35.

128. Mourier A, Gautier JF, De Kerviler E, et al. Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements. Diabetes Care. 1997;20:385-91.

129. Eriksson J, Tuominen J, Valle T et al. Aerobic endurance exercise or circuit-type resistance training for individuals with impaired glucose tolerance? Horm Metab Res. 1998;30:37-41.

130. Brandenburg SL, Reusch JE, Bauer TA et al. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care. 1999;22:1640-6.

131. Tessier D, Menard J, Fulop T et al. Effects of aerobic physical exercise in the elderly with type 2 diabetes mellitus. Arch Gerontol Geriatr. 2000;31:121-132.

132. Rigla M, Fontcuberta J, Mateo J et al. Physical training decreases plasma thrombomodulin in type I and type II diabetic patients. Diabetologia. 2001;44:693-9.

133. Gerstenblith G, Frederiksen J, Yin FC, et al. Echocardiographic assessment of a normal adult aging population. Circulation. 1977;56:273-8.

134. Pluim BM, Zwinderman AH, van der Laarse A, et al. The athlete's heart. A meta-analysis of cardiac structure and function. Circulation. 2000;101:336-44.

135. Kokkinos PF, Narayan P, Colleran JA et al. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. N Engl J Med. 1995;333:1462-7.

136. Turner MJ, Spina RJ, Kohrt WM et al. Effect of endurance exercise training on left ventricular size and remodeling in older adults with hypertension. J Gerontol A Biol Sci Med Sci. 2000;55:M245-51.

137. Baglivo HP, Fabregues G, Burrieza H et al. Effect of moderate physical training on left ventricular mass in mild hypertensive persons. Hypertension. 1990;15:I153-6.

138. Wirth A, Kroger H. Improvement of left ventricular morphology and function in obese subjects following a diet and exercise program. Int J Obes Relat Metab Disord. 1995;19:61-6.

139. Hinderliter A, Sherwood A, Gullette EC et al. Reduction of left ventricular hypertrophy after exercise and weight loss in overweight patients with mild hypertension. Arch Intern Med. 2002;162:1333-9.

140. Peterson LR, Rinder MR, Schechtman KB et al. Peak exercise stroke volume: associations with cardiac structure and diastolic function. J Appl Physiol. 2003;94:1108-14.

141. Kitzman DW, Sheikh KH, Beere PA et al. Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. J Am Coll Cardiol. 1991;18:1243-50.

142. Forman DE, Manning WJ, Hauser R et al. Enhanced left ventricular diastolic filling associated with long-term endurance training. J Gerontol. 1992; 47:M56-8.

143. Douglas PS, O'Toole M. Aging and physical activity determine cardiac structure and function in the older athlete. J Appl Physiol. 1992;72:1969-73.

144. Takemoto KA, Bernstein L, Lopez JF et al. Abnormalities of diastolic filling of the left ventricle associated with aging are less pronounced in exercise-trained individuals. Am Heart J. 1992;124:143-8.

145. Levy WC, Cerqueira MD, Abrass IB et al. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. Circulation. 1993;88:116-26.

146. Spina RJ, Miller TR, Bogenhagen WH et al. Gender-related differences in left ventricular filling dynamics in older subjects after endurance exercise training. J Gerontol A Biol Sci Med Sci 1996;51:B232-B237.

147. Mier CM, Turner MJ, Ehsani AA et al. Cardiovascular adaptations to 10 days of cycle exercise. J Appl Physiol 83: 1900-1906, 1997.

148. Spina RJ, Turner MJ, Ehsani AA. β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am J Physiol Heart Circ Physiol. 1998;274: H397-H404.

149. Spina RJ, Rashid S, Davila-Roman VG et al. Adaptations in beta-adrenergic cardiovascular responses to training in older women. J Appl Physiol. 2000;89:2300-5.

150. Beere PA, Russell SD, Morey MC et al. Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men. Circulation. 1999;100:1085-94.

151. Eugene M, Vandewalle H, Bertholon JF et al. Arterial elasticity and physical working capacity in young men. J Appl Physiol. 1986;61:1720-3.

152. Cameron JD, Rajkumar C, Kingwell BA et al. Higher systemic arterial compliance is associated with greater exercise time and lower blood pressure in a young older population. J Am Geriatr Soc. 1999;47:653-6.

153. Rywik TM, Blackman MR, Yataco AR et al. Enhanced endothelial vasoreactivity in endurance-trained older men. J Appl Physiol. 1999;87:2136-42.

154. Rinder MR, Spina RJ, Ehsani AA. Enhanced endothelium-dependent vasodilation in older endurance-trained men. J Appl Physiol. 2000;88:761-6.

155. Vaitkevicious PV, Fleg JL, Engel JH et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation. 1993;88:1456–1462.

156. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler Thromb Vasc Biol. 1998;18:127–132.

157. Tanaka H, Dinenno FA, Monahan KD et al. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 2000;102:1270-5.

158. DeSouza CA, Shapiro LF, Clevenger CM et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000;102:1351-7.

159. Taddei S, Galetta F, Virdis A et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. Circulation. 2000;101:2896-901.

160. Maiorana A, O'Driscoll G, Cheetham C et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001, 38:860-6.

161. Folsom AR, Eckfeldt JH, Weitzman S et al. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Stroke. 1994;25:66-73.

162. Olsen MH, Wachtell K, Hermann KL et al. Maximal exercise capacity is related to cardiovascular structure in patients with longstanding hypertension. A LIFE substudy. Losartan Intervention For Endpoint-Reduction in Hypertension. Am J Hypertens. 2001;14:1205-10.

163. Tanaka H, Seals DR, Monahan KD et al. Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. J Appl Physiol. 2002;92:1458-64.

164. Moreau KL, Donato AJ, Seals DR et al. Arterial intima-media thickness: site-specific associations with HRT and habitual exercise. Am J Physiol Heart Circ Physiol. 2002;283:H1409-17.

165. Schmidt-Trucksass, AS, Grathwohl D et al. Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis. 1999;145:107-114.

166. Dinenno FA, Tanaka H, Monahan KD et al. Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. J Physiol. 2001;534:287-95.

167. Ferrier KE, Waddell TK, Gatzka CD et al. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension. 2001;38:222-6.

168. Snell PG, Martin WH, Buckey JC, et al. Maximal vascular leg conductance in trained and untrained men. J Appl Physiol. 1987;62:606-10.

169. Lavrencic A, Salobir BG, Keber I. Physical training improves flow-mediated dilation in patients with the polymetabolic syndrome. Arterioscler Thromb Vasc Biol. 2000; 20:551-5.

170. Higashi Y, Sasaki S, Kurisu S et al. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. Circulation. 1999; 100:1194-202.

171. Hambrecht R, Hilbrich L, Erbs S et al. Correction of endothelial dysfunction in chronic heart failure: additional effects of exercise training and oral L-arginine supplementation. J Am Coll Cardiol. 2000; 35:706-13.

172. Hambrecht R, Wolf A, Gielen S et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med. 2000; 342:454-60.

173. Maiorana A, O'Driscoll G, Dembo L et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol. 2000; 279:H1999-2005.

174. Gielen S, Erbs S, Linke A et al. Home-based versus hospital-based exercise programs in patients with coronary artery disease: effects on coronary vasomotion. Am Heart J. 2003;145:E3.

175. Mokdad AH, Ford ES, Bowman BA et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:76-9.

176. Neel JV. The "thrifty genotype" in 1998. Nutr Rev. 1999;57:S2-9.

Chapter II.
Study I
Cardiovascular adaptations to aerobic and strength training in older women

INTRODUCTION

Aging is associated with a decline in cardiorespiratory fitness at a rate of ~10% per decade[1,2], secondary to an age-related decline in cardiac output reserve[3-5]. As these declines are attenuated with aerobic exercise training[6-8] it has been proposed that age-related cardiovascular dysfunction is more a function of deconditioning and less a function of senescence[9]. The mechanism (s) through which exercise attenuates the age-related decline in cardiorespiratory fitness is not uniform however, and gender differences in the cardiovascular adaptations to exercise training in older men and women have been reported [reviewed in 10]. Where both genders improve VO_{2max} with endurance training the changes in left ventricular geometry and function observed with exercise training in men[11-13], have not been observed in women[14-17].

It is possible that exercise capacity in older women is limited not by oxygen delivery, but rather by muscular strength. In support of this statement, Fleg and Lakatta[18] have demonstrated a significant relationship between creatinine excretion (a marker of muscle atrophy) and cardiorespiratory fitness ($r = 0.47$, $p < 0.001$) in healthy older women. It is therefore, possible that age-related sarcopenia could limit muscular strength and power output reducing the ability to attain the upper limits of cardiovascular flux, in older women. Inasmuch, interventions that improve muscular strength could elicit improvements in cardiorespiratory fitness in older women, without any appreciable change in cardiac structure or function. To date however, there is a paucity of information examining the independent effects of interventions designed to target cardiovascular or muscular limitations to exercise capacity in healthy older women. The purpose of this investigation was therefore to examine the cardiovascular adaptations to aerobic (AT) and strength training (ST) on cardiorespiratory fitness in healthy older women.

METHODS

The subjects for this investigation consisted of 34 healthy post menopausal women (68 ± 4 yrs) who met the following criteria: 1) no clinical evidence of cardiovascular disease; 2) normal ECG at rest and at peak exercise 3) not currently taking cardiovascular medications (i.e. antihypertensives); 4) no regular (>3 days/week)

participation in endurance or strength training and 5) absence of cerebrovascular or orthopedic disability that would limit exercise training. Initial baseline testing consisted of a graded maximal exercise test to assess cardiorespiratory fitness, maximal strength testing and resting echocardiograms. Subjects were recruited from the local Edmonton area. Informed consent was obtained from all subjects prior to the investigation and the Research Ethics Review Board within the Faculty of Medicine at the University of Alberta approved the study protocol.

Graded exercise test to exhaustion

Oxygen consumption, carbon dioxide production and minute ventilation were sampled every five seconds at rest and during exercise using a Parvo Medics TrueMax 2400 Metabolic Cart (Parvo Medics, East Sandy, UT). Exercise was performed on a cyucle ergometer, beginning at a workload of 30 watts and increasing by 15 watts every two minutes until volitional exhaustion. Heart rate (12 lead ECG), blood pressure (auscultation) and a rating of perceived exertion (Borg scale) was determined at the end of each stage. Subjects were encouraged to continue exercising until respiratory exchange ratio exceeded 1.15 and/or heart rate was within 5 beats of age-predicted maximum.

Cardiorespiratory fitness ($\dot{V}O_{2peak}$) was considered the peak rate of oxygen consumption during the last 60 seconds of the graded exercise test. The heart rate response to graded exercise was used to prescribe exercise intensity during the exercise intervention.

Maximal strength

Upper and lower extremity maximal strength were assessed as a voluntary one-repetition maximum (1RM) using the following exercises on a nautilus machine: 1) leg press; 2) leg extension; 3) leg curl; 4) chest press; 5) shoulder press; 6) latissimus dorsi pull down; 7) triceps pushdown; 8) unilateral arm curls. The 1RM tests were repeated within a one-week period and the heaviest weight lifted while adhering to strict technique was used as the baseline 1RM.

Echocardiographic Measurements

Imaging of the left ventricle (LV) was performed as previously described[19-21]. In brief, all images were captured using a commercially available ultrasound instrument (Hewlett Packard, Sonos 5500) with a 3.5 MHz transducer. Two-dimensional transthoracic images of the LV were obtained at rest from the parasternal short-axis view at the level of the mid-papillary muscles according to American Society of Echocardiography guidelines[19]. All measurements were performed by a trained technician. LV morphology was estimated from previously published formulas[20]. LV diastolic filling dynamics were assessed using pulsed-wave Doppler analysis of transmitral and pulmonary venous flow patterns recorded in the apical four chamber view[21]. All echocardiographic images were averaged over three cardiac cycles.

Randomization and Exercise training

Following baseline testing, subjects were randomized to either AT, ST, combined aerobic and strength training (CmT) or a control (CT) group. All three groups performed three exercise sessions per week for a duration of 12 weeks, under supervision, in the Therapeutic Exercise Laboratory within the Faculty of Rehabilitation Medicine at the University of Alberta. AT was performed on a cycle ergometer for an initial duration of 15 minutes and increasing by 2.5 minutes each week up to a maximal duration of 42.5 minutes of moderate cycling at between 65 and 75% of heart rate reserve. ST consisted of three sets of 10-12 repetitions performed on large muscle groups tested at 50-65% of 1RM on large muscle groups. Specifially those in the ST amd CmT group performed chest press, leg press, lat pulldown, shoulder press, leg extension, leg curl, tricep pushdown and arm curls. 1RM testing was repeated every 4 weeks to ensure appropriate training intensities. CmT performed both AT and ST training programs. Participants in the CT group were advised to continue performing activities of daily living throughout the intervention time period. Baseline testing was repeated following the 12-week intervention time period in all four groups.

Statistical analysis

Statistical analysis was performed with a two-way repeated measures ANOVA using SPSS software, (Chicago, IL). The absolute change following exercise training for

all outcome measures was performed with a one-way ANOVA. If a significant effect was found then a Tukey LSD significance test was performed. The alpha level was set at $p<0.05$.

RESULTS

Baseline characteristics are provided in Table 1. Of the 34 women tested 31 completed the investigation (AT = 8; ST = 8; CmT = 6; CT = 9). Three women withdrew due to either time constraints (n=2), or injury unrelated to the study (n=1). There were no differences between the groups in age, VO_{2peak}, maximal heart rate or peak power output at baseline (Table 1).

Exercise training did not elicit an appreciable change in body mass in any of the three exercise training groups. Peak power output and VO_{2peak} increased significantly with all three forms of training and remained unchanged in the CT group (Table 1). Absolute and relative VO_{2peak} values increased 10, 13 and 20% in the AT, ST and CmT groups respectively, (Figures 1&2. $p < 0.05$ vs pre training in all groups). The delta change in absolute and relative VO_{2peak} was approximately 40% higher ($p < 0.05$) in the CmT group compared to either AT or ST alone.

Maximal strength increased in all muscle groups tested, save the biceps and triceps in the ST and CmT groups. AT and CT did not observe any change in muscle strength in any of the muscle groups tested. A weak positive relationship ($r = 0.387$, $p < 0.057$) was observed between the change in leg strength and the improvement in VO_{2peak} with exercise training when all subject data was pooled (Figure 3).

Peak ventilation increased significantly following ST and CmT but not AT or CT (Table 2). The improvement in peak ventilation was only significantly greater in the ST and CmT groups (Figure 4). A strong positive relationship was observed between the change in peak ventilation and VO_{2peak} ($r = 0.79$, $P < 0.001$) when all subject data was pooled (Figure 5)

There was no significant change in LV geometry or size, systolic performance or filling dynamics with any training intervention (Table 2).

DISCUSSION

The novel finding of this investigation is that 12 weeks of ST is as effective as AT for increasing VO_{2peak}, despite no change in cardiac structure or function. A second finding is that the improvement in VO_{2peak} with CmT was significantly greater than following AT or ST performed alone, suggesting that the effects of AT and ST on cardiovascular function may be additive.

AT has consistently been shown to improve VO_{2peak} in healthy older men and women (reviewed in 10). Twelve weeks of AT alone elicited a 10% improvement in VO_{2peak} in healthy older women. Similar to previous investigations[14-17], this was observed without any appreciable change in body mass or resting cardiac structure or function. Interestingly, the improvements in VO_{2peak} observed with AT were equivalent to that observed with ST alone.

Improvements in VO_{2peak} ranging from 5-25% have been documented following ST alone, in several[22-25] but not all [8] studies in older individuals. The improvements in VO_{2peak} with ST in older men or women have been attributed to increased mitrochondrial oxidative enzyme activity[23], muscle capilarization[23,24], and increased type I fiber content[24]. Vincent and colleagues[25] recently reported improvements of 20.9 and 24% in VO_{2peak} following six months of low and high intensity ST in a mixed cohort of older healthy individuals. They hypothesized that the improvement in VO_{2peak} with ST in healthy older women was a function of increased muscle strength. Specifically, they believed that improved muscle strength permitted greater workloads to be attained during maximal exercise tests and therefore a greater recruitment of cardiovascular reserve. They also observed significant relationships between muscular strength (leg press, leg curl, leg extension) and VO_{2peak} in healthy older women. These relationships have been demonstrated by others as well[26] and support the concept that muscular strength may be a limitation to achieving maximal rates of oxygen consumption in healthy older individuals. The data presented here support these findings, as improvements in VO_{2peak} were observed following only CmT and ST alone. Furthermore a weak relationship was observed between the change in VO_{2peak} and the change in maximal leg press strength following training. It is therefore likely that improvements in VO_{2peak} with ST and AT in healthy older women occur via different mechanisms.

To our knowledge only one other investigation has examined the effects of AT and CmT on cardiorespiratory fitness and cardiac function in healthy older women. Ferketch *et al*[23] compared the effects of 12 weeks of AT versus CmT on VO_{2peak}, and cardiac function at rest and during submaximal exercise in healthy older women. Interestingly, improvements in VO_{2peak} were observed without any changes in cardiac output or arterio-venous oxygen difference at rest or during submaximal exercise. Taken together these data would suggest that, in older women, improvements in cardiorespiratory fitness were more a function of an increase in muscular strength rather than a cardiovascular adaptation. Our data provide additional information as ST alone, elicited improvements in VO_{2peak} similar to those observed with AT in the absence of any change in cardiac structure or function.

Previous investigations have documented gender differences in the cardiovascular responses to exercise training[14-16]. Specifically, where males tend to rely on structural and functional changes in cardiac performance with AT[10-13], women do not[16,17]. Our data support the work of Spina[14-17], that have clearly demonstrated that as much as 12 months of AT has little effects of LV structure, systolic or diastolic performance in previously sedentary older women. Our data support these findings and extend them to ST and CmT interventions. Therefore there is now strong evidence to suggest that exercise training in any form is not associated with changes in cardiac structure or function in older women.

An increase in muscular strength following ST in older women is a common observation[22-25,27]. With regards to maximal strength, 30 and 55% increases in leg press maximal strength were observed following ST and CmT respectively. These are in line with previous investigations in older women of similar age (73 ± 1 yrs), and following similar training duration (16 weeks)[27]. Interestingly, leg strength remina unchanged following AT. This is contrary to a recent investigation that has documented improvements in leg extension maximal strength with AT[23]. It is possible that aerobic exercise intensity prescribed in our investigation may not have been of sufficient intensity to elicit any changes in muscle recruitment patterns or morphology. Furthermore, the neural adaptations which may have occurred during cycling that would lead to an increase in leg strength are not likely measurable with leg press or leg extension

exercises. Similar to others[23,27], improvements in muscular strength with ST or CmT led to a significant improvement in exercise performance (i.e. an increase in peak power output achieved during a maximal exercise test). Our data extend previous observations as we demonstrate that these adaptations were achieved without any measurable adaptations in cardiac structure or function.

One of the most interesting observations in this investigation was the increase in peak ventilation with ST and CmT. Yerg and colleagues[28] have demonstrated that maximal ventilation is higher in older masters athletes and increases with 12 months of endurance training in previously sedentary men and women 63 ± 1 yrs. In a subsequent study they demonstrated that maximal ventilation increased significantly following AT but was unchanged with ST[8]. This work adds to the concept that older healthy individuals who exercise regularly maintain their ventilatory reserve and "underscore the permissive role of the respiratory system in regulating improvements in VO_{2peak} with exercise training". Aging is associated with mechanical constraints to ventilation that result in an increase in end-expiratory lung volume and expired airflow limitation[29]. It is therefore possible that ST or CmT improves respiratory muscle strength and subsequently attenuates reductions in airflow limitation associated with aging, thereby increasing ventilation at maximal exercise. It is also possible that an increase in muscular strength with ST or CmT, increases the ability to attain higher workloads during a maximal exercise test and therefore results in an increased maximal ventilation.

The primary limitation to this investigation is that we did not assess cardiovascular function under stress, such as exercise or β-adrenergic stimulation. As a result it is unclear whether exercise training was associated with an improvement in left ventricular function or blood flow distribution at maximal exercise in healthy older women. A second limitation to this investigation is that we did not control for changes in peripheral cardiovascular function that could explain improvements in VO_{2peak} with exercise training in older women. It is therefore possible that improvements in blood flow distribution, capillary density or capillary recruitment with exercise training could explain these results[23,27]. Finally, the duration of the investigation may have been of insufficient duration to result in the most optimal improvement in cardiac structure or

function. We believe this is unlikely as previous studies in healthy older women[17] have found similar results following as much as 12 months of AT.

The findings of this investigation have significant clinical application in the area of exercise therapy in the aged. The observation that improvements in VO_{2peak} with AT and ST were similar, suggest that ST may be as effective as AT in attenuating the age-related decline in exercise capacity in older women. Secondly the observation that the improvement in VO_{2peak} with CmT was ~40% greater than ST or AT, suggests that the effects of each type of training may be additive. Therefore, although AT is commonly regarded as the most beneficial type of exercise training for older individuals, ST should be included into exercise training programs for older women.

In conclusion, the findings of the present study demonstrate that improvements in VO_{2peak} associated with AT and ST are similar, possibly additive and occur independent of any change in resting cardiac structure or function, in healthy older women.

REFERENCES

1. Astrand I. Aerobic work capacity in men and women with special reference to age. Acta Physiol Scand. 1960;49(suppl 169):1–92.

2. Hagberg JM. Effect of training on the decline of VO_2 max with aging. Fed Proc. 1987;46:1830–1833.

3. Higginbotham MB, Morris KG, Williams RS, Coleman RE, Cobb FR. Physiologic basis for the age-related decline in aerobic work capacity. Am J Cardiol. 1986; 57:1374–1379.

4. Granath A, Jonsson B, Strandell T. Circulation in healthy old men, studied by right heart catheterization at rest and during exercise in supine and sitting position. Acta Med Scand. 1964;176:425–446.

5. Ogawa T, Spina RJ, Martin WH III, Kohrt WM, Schechtman KB, Holloszy JO, Ehsani AA. Effects of aging, sex and physical training on cardiovascular responses to exercise. Circulation. 1992;86:494–503.

6. Dehn MM, Bruce RA. Longitudinal variations in maximal oxygen intake with age and activity. J Appl Physiol. 1972;33:805–807.

7. Hurley BF, Ehsani AA, Holloszy JO. A hemodynamic comparison of young and older endurance athletes during exercise. J Appl Physiol. 1985;58:2041–2046.

8. Hagberg JM, Graves JE, Limacher M, Woods DR, Leggett SH, Cononie C, Gruber JJ, Pollock ML. Cardiovascular responses of 70- to 79-yr-old men and women to exercise training. J Appl Physiol. 1989;66:2589–2594.

9. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bedrest and Training Study: II. Effect of age on cardiovascular adaptation to exercise training. Circulation. 2001;104:1358-66.

10. Spina RJ. Cardiovascular adaptations to endurance exercise training in older men and women. Exerc Sport Sci Rev. 1999;27:317-32.

11. Seals DR, Hagberg JM, Spina RJ, Rogers MA, Schechtman KB, Ehsani AA. Enhanced left ventricular performance in endurance trained older men. Circulation. 1994;89:198-205.

12. Spina RJ, Turner MJ, Ehsani AA. Exercise training enhances cardiac function in response to an afterload stress in older men. Am J Physiol. 1997;272:H995-1000.

13. Spina RJ, Turner MJ, Ehsani AA. Beta-adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am J Physiol. 1998;274:H397-404.

14. Spina RJ, Miller TR, Bogenhagen WH, Schechtman KB, Ehsani AA. Gender-related differences in left ventricular filling dynamics in older subjects after endurance exercise training. J Gerontol A Biol Sci Med Sci. 1996;51:B232-7.

15. Turner MJ, Mier CM, Spina RJ, Schechtman KB, Ehsani AA. Effects of age and gender on the cardiovascular responses to isoproterenol. J Gerontol A Biol Sci Med Sci.1999;54:B393-400.

16. Spina RJ, Ogawa T, Kohrt WM, Martin WH 3rd, Holloszy JO, Ehsani AA. Differences in cardiovascular adaptations to endurance exercise training between older men and women. J Appl Physiol. 1993;75:849-55.

17. Spina RJ, Rashid S, Davila-Roman VG, Ehsani AA. Adaptations in beta-adrenergic cardiovascular responses to training in older women. J Appl Physiol. 2000;89:2300-5.

18. Fleg JL and Lakatta EG. Role of muscle loss in the age-associated reduction in VO2 max. J Appl Physiol 1988;65: 1147-1151.

19. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978;58:1072-83.

20. Reichek N, Devereux RB. Reliable estimation of peak left ventricular systolic pressure by M-mode echographic-determined end-diastolic relative wall

thickness: identification of severe valvular aortic stenosis in adult patients. Am Heart J 1982;103:202-3.

21. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG . Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care. 2001;24:5-10.

22. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of VO2max in older men.J Appl Physiol. 1990;68:329-33.

23. Ferketich AK, Kirby TE, and Alway SE. Cardiovascular and muscular adaptations to combined endurance and strength training in elderly women. Acta Physiol Scand 1998;164: 259-267.

24. Hepple RT, Mackinnon SL, Goodman JM, Thomas SG, Plyley MJ. Resistance and aerobic training in older men: effects on VO2peak and the capillary supply to skeletal muscle. J Appl Physiol. 1997;82:1305-10.

25. Vincent KR, Braith RW, Feldman RA, Kallas HE, Lowenthal DT. Improved cardiorespiratory endurance following 6 months of resistance exercise in elderly men and women. Arch Intern Med. 2002 ;162:673-8.

26. Kostka T, Rahmani A, Berthouze SE, Lacour JR, Bonnefoy M. Quadriceps muscle function in relation to habitual physical activity and VO2max in men and women aged more than 65 years. J Gerontol A Biol Sci Med Sci. 2000;55:B481-8.

27. Fielding RA, LeBrasseur NK, Cuoco A, Bean J, Mizer K, Singh MAF High-velocity resistance training increases skeletal muscle peak power in older women. Journal of the American Geriatrics Society 2002;50: 655-662.

28. Yerg JE 2nd, Seals DR, Hagberg JM, Holloszy JO. Effect of endurance exercise training on ventilatory function in older individuals. J Appl Physiol. 1985;58:791-4.

29. DeLorey DS, Babb TG. Progressive mechanical ventilatory constraints with aging. Am J Respir Crit Care Med. 1999;160:169-77.

List of tables and figures

Table 1. Baseline characteristics and the effects of different types of training on selected variables at peak exercise.

(Values are mean ± SE; all comparison p>0.05)
† = p < 0.05 vs pre

Table 2. Effects of different types of training on LV morphology, mass and diastolic filling

AT = Aerobic trained; ST = Strength trained; CmT = Combined aerobic and strength trained; CT = Control group

(Values are mean ± SE; all comparison p>0.05)
† = p < 0.05 vs pre

Figure 1. Improvement in relative VO_{peak} following different types of training in healthy older women. * = p < 0.05

Figure 2. Improvement in absolute VO_{peak} following different types of training in healthy older women. * = p < 0.05

Figure 3. Relationship between relative improvement in leg press maximal strength and VO_{2peak} in healthy older women.

Figure 4. Improvement in maximal ventilation following different types of exercise trainig in healthy older women. * = p < 0.05

Figure 5. Relationship between the change in maximal ventilation and VO_{2peak} with exercise training in healthy older women.

AT = Aerobic trained; ST = Strength trained; CmT = Combined aerobic and strength trained; CT = Control group

Table 1

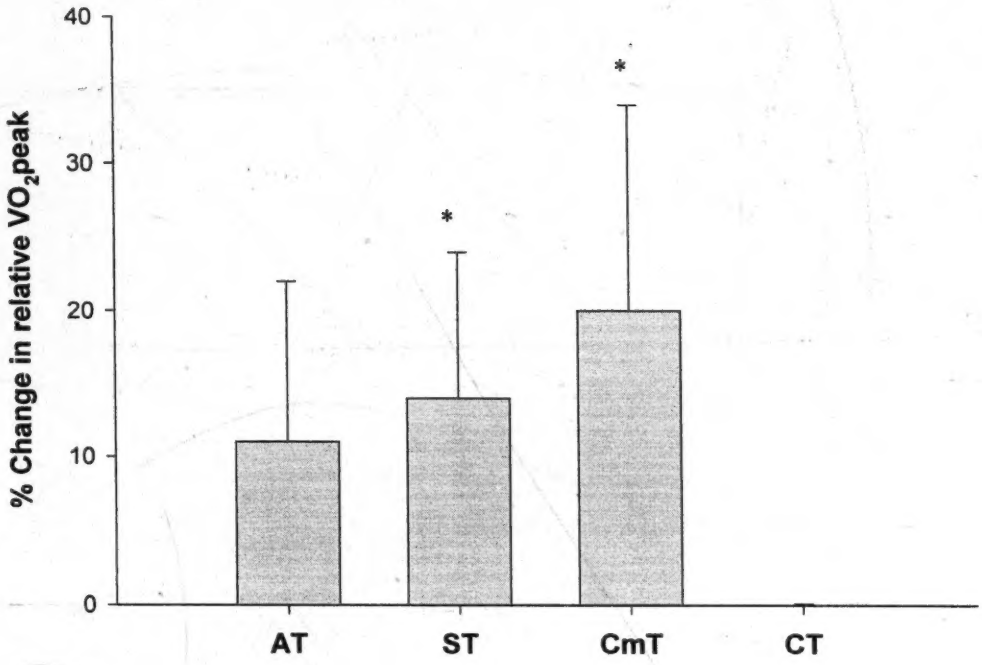
	Time	AT (n= 8)	ST (n= 8)	CmT (n= 6)	CT (n = 9)
Age (years)		66 ± 1	70 ± 1	68 ± 2	67 ± 1
BMI (kg/m^2)	Pre	28.3 ± 6.2	28.0 ± 6.8	28.0 ± 4.0	28.7 ± 6.3
	Post	28.2 ± 6.5	28.2 ± 6.4	27.3 ± 5.0	28.7 ± 4.9
Power output (Watts)	Pre	107 ± 7.6	88 ± 5	96 ± 13	95 ± 5
	Post	120 ± 6.5†	105 ± 7†	123 ± 11†	95 ± 4.0
VO_{2peak} (ml/kg/min)	Pre	22.3 ± 0.9	21.2 ± 1.6	21.0 ± 1.3	21.1 ± 0.8
	Post	24.6 ± 0.7†	23.9 ± 1.3†	25.2 ± 2.1†	20.7 ± 0.4
$V_{E\ peak}$ (L/min)	Pre	70 ± 5	59 ± 4	59 ± 9	63 ± 5
	Post	69 ± 5	69 ± 5†	67 ± 4†	57 ± 3
HR_{peak} (Beats/min)	Pre	155 ± 5	157 ± 3	159 ± 8	157 ± 6
	Post	160 ± 3	160 ± 6	162 ± 6	154 ± 6

† = $p < 0.05$ vs pre

Table 2

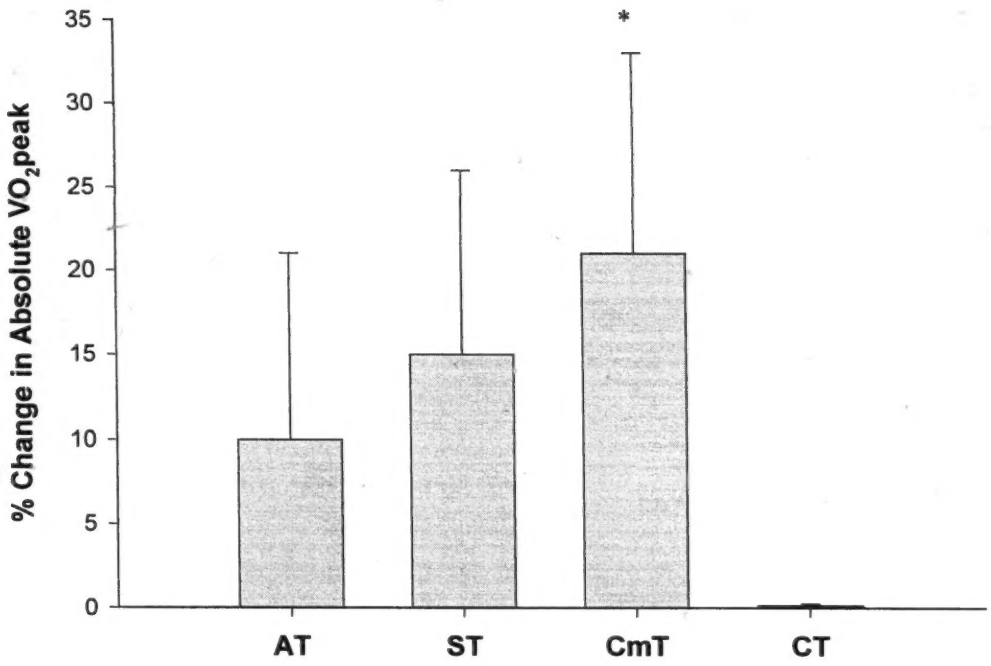
	Time	AT (n= 8)	ST (n= 8)	CmT (n= 6)	CT (n = 9)
Relative wall thickness	Pre	0.39 ± 0.40	0.41 ± 0.30	0.40 ± 0.40	0.41 ± 0.20
	Post	0.41 ± 0.40	0.37 ± 0.20	0.33 ± 0.20	0.44 ± 0.30
LV mass (g/m^2)	Pre	72.0 ± 4.1	68.0 ± 4.3	66.0 ± 4.7	82.0 ± 3.8
	Post	68.0 ± 3.9	73.2 ± 4.9	68.4 ± 2.7	78.0 ± 8.2
LV end-systolic wall stress (g/cm^2)	Pre	34.1 ± 2.2	35.8 ± 5.7	39.8 ± 5.7	33.2 ± 1.5
	Post	34.0 ± 5.3	37.5 ± 7.1	45.0 ± 5.7	32.6 ± 4.5
E/A ratio	Pre	1.11 ± 0.0	0.92 ± 0.1	1.04 ± 0.1	0.78 ± 0.0
	Post	1.08 ± 0.1	1.03 ± 0.1	0.99 ± 0.1	0.88 ± 0.1

Figure 1.



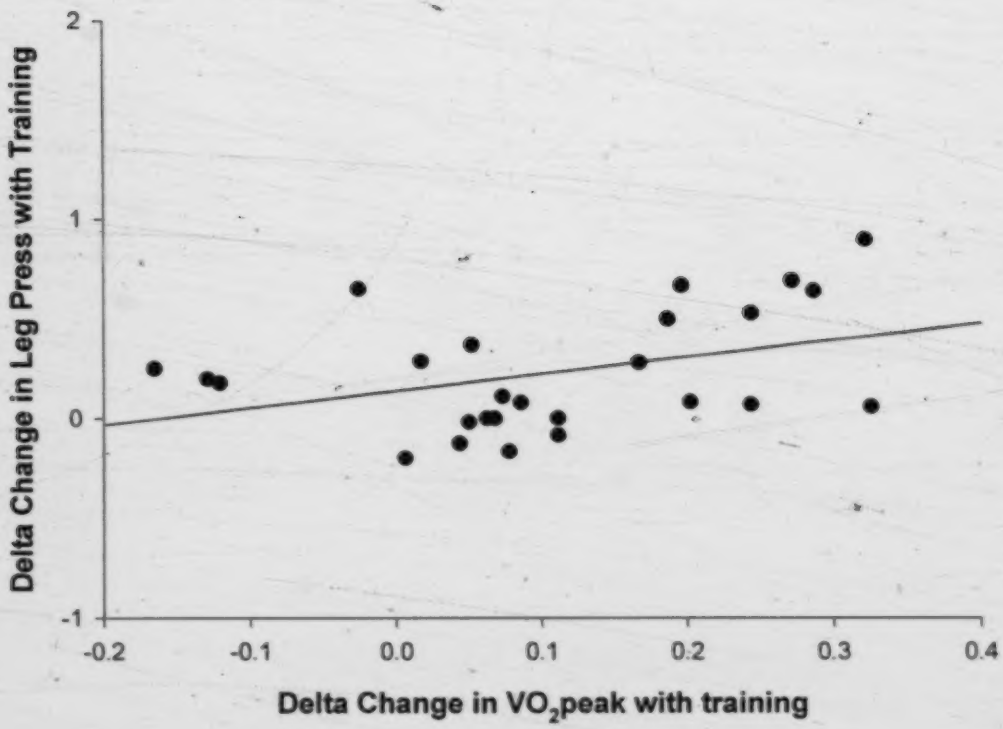
* = $p < 0.05$ vs control

Figure 2.



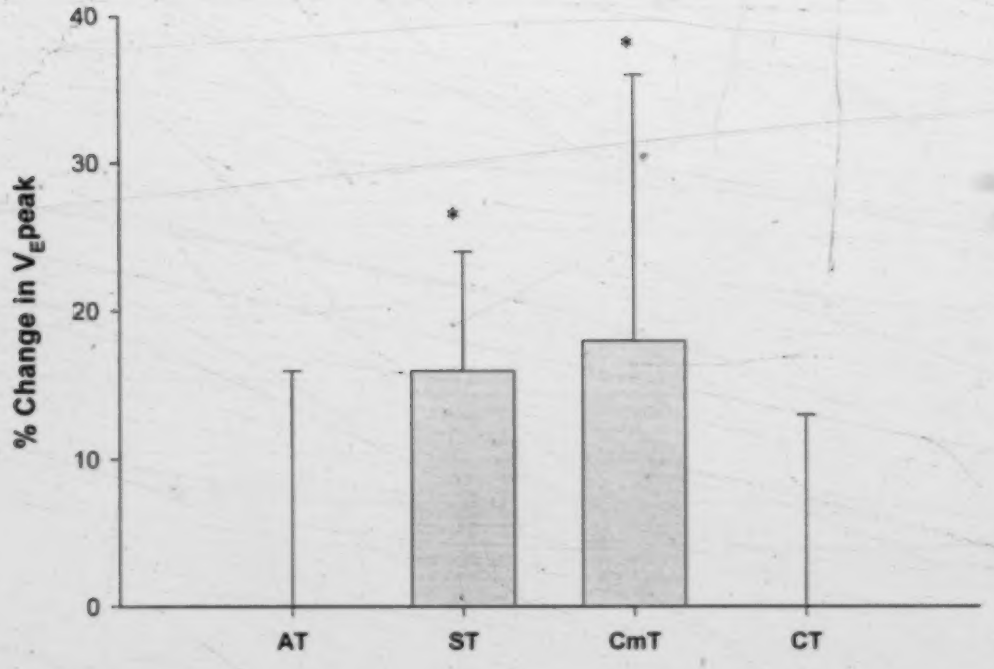
* = $p < 0.05$ vs control

Figure 3.



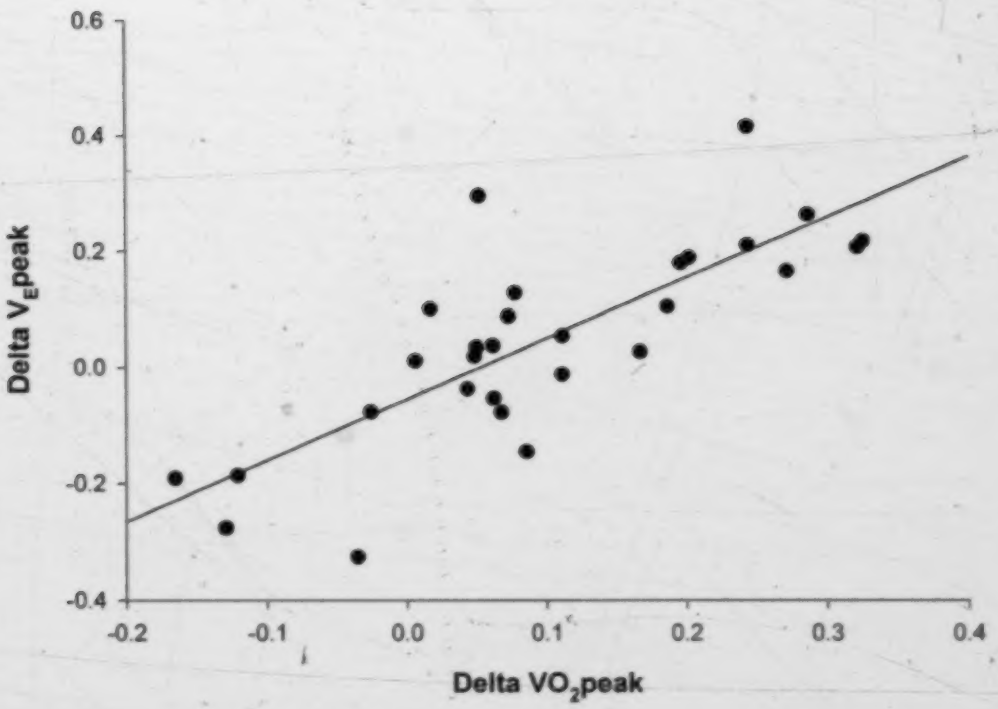
$r = 0.378$, $p < 0.057$

Figure 4.



* = $p < 0.05$ vs control

Figure 5.



r=0.79, r^2 = 0.62 p < 0.001

Chapter III.

Study II

Effects of Exercise Training on Left Ventricular Structure and Function and Arterial Compliance in Women with Type 2 Diabetes

INTRODUCTION

Type 2 diabetes (DM-2) is associated with an increased risk in the development of cardiovascular disease (CVD)[1] with macrovascular disease accounting for up to 80% of all deaths in this population[2,3]. This may be related to a decline in arterial compliance and it's components in persons with insulin resistance or DM-2[4-6]. Since arterial compliance is currently becoming recognized as a potentially modifiable CVD risk factor[7-9], interventions that improve arterial compliance may be beneficial in reducing the incidence of CVD in persons with DM-2. The observation that arterial compliance correlates well with cardiorespiratory fitness[10-13], suggests that exercise training may be an important adjunct in the treatment and prevention of CVD in persons with DM-2[14].

Type 2 diabetes mellitus is also associated with an increased risk for the development of heart failure[15]. This maybe related to functional, biochemical, and morphological left ventricular (LV) abnormalities associated with DM-2[16-18]. The most common cardiac abnormality associated with the diabetic state is a reduction in LV diastolic filling[19,20]. Not only is a reduction in LV filling dynamics associated with reduced exercise capacity[21,22], but it is also associated with an increased mortality risk[23].

Exercise training has been shown to reduce the risk for CVD as well as improve functional capacity in healthy populations[24]. This may be explained through exercise-mediated improvements in vascular function[11] and/or LV filling dynamics[25]. Exercise training has been shown to elicit improvements in cardiorespiratory fitness in persons with DM-2[26]. Enhanced cardiorespiratory fitness is associated with a reduction in all-cause mortality in DM-2 [27], however, the underlying mechanisms for this adaptation have yet to be examined. It is possible that the underlying mechanisms responsible for this adaptation may be cardiac and/or vascular in nature.

Currently, there is a lack of scientific evidence describing the effects of exercise training on measures of cardiovascular function in persons with DM-2. The purpose of this investigation was to examine the effects of exercise training on cardiorespiratory fitness, arterial compliance and LV filling dynamics in women with DM-2. Women were chosen for this study as current literature suggests that women are at a greater risk for CVD once diagnosed with DM-2, compared to men[28-30].

METHODS

Subjects

Sixteen older women (56 ± 4yrs) with DM-2, free from diabetic complications, were screened for underlying coronary artery disease with resting and maximal exercise electrocardiograms. has assessed with chart review. Presence of DM-2 and diabetes-related complications were confirmed by chart review. Individuals in this investigation were treated for diabetes through diet and exercise or oral hypoglycemic agents, no participants were on insulin therapy. Several subjects were taking lipid lowering or antihypertensive medications during the investigation period. Exclusion criteria for this investigation included: HbA_{1c} levels > 9%; evidence of ischemic heart disease by history or by resting or exercise electrocardiogram (ECG) (>1.5 mm flat or down sloping ST segment depression); angina or any other cardiac symptoms potentially limiting exercise capacity; presence of musculoskeletal or peripheral vascular abnormalities that would limit exercise capacity. Informed consent was obtained from all subjects prior to the investigation and the Research Ethics Review Board at the University of Alberta approved the study protocol.

Study protocol

Prior to exercise training, subjects were evaluated over the course of three separate visits. Initially, patients reported to the Division of Cardiology within the University of Alberta Hospital for a history and physical examination as well as a resting and exercise ECG. The graded exercise test was performed on an electronically braked cycle ergometer to determine ventilatory threshold and cardiorespiratory fitness. On a second visit, subjects reported to the Metabolic Unit within the University of Alberta Hospital following an overnight fast for blood work, applanation tonometry and resting echocardiograms. On a third day patients reported to the Therapeutic Exercise laboratory within the Faculty of Rehabilitation Medicine for strength testing and familiarization with the exercise equipment.

Graded exercise test to exhaustion

Testing began with the subject on a cycle ergometer for resting ECG and ventilatory measurements. Oxygen consumption, carbon dioxide production and minute ventilation were sampled breath by breath at rest and during exercise and values were averaged every 15 seconds using a MedGraphics Metabolic Cart (Medical Graphics, Minneapolis, MN). The initial work rate was set at 30 Watts and participants were asked to maintain a pedal cadence between 50 and 70 rpm throughout the test, while the work rate was increased in 15-Watt increments every two minutes until exhaustion. The duration of the test ranged from 12 and 20 minutes. Peak rate of oxygen consumption (VO_{2peak}) was determined from the average rate of oxygen consumption over the final 60 seconds of the graded exercise test. Arm blood pressure (auscultation) was performed according to American Heart Association guidelines and heart rate was determined from 12-lead ECG recordings.

Maximal Strength Testing

Upper and lower extremity maximal strength were assessed as a voluntary one-repetition maximum using the following exercises: 1) leg press; 2) leg extension; 3) leg curl; 4) chest press; 5) shoulder press; 6) latissimus dorsi pull down; 7) triceps pushdown; 8) unilateral arm curls. The 1RM tests were repeated within a one-week period and the heaviest weight lifted while adhering to strict technique was used as the baseline maximal strength.

Exercise Training

Each subject exercised 3 times per week for a duration of 10 weeks, under supervision, in the Therapeutic Exercise Laboratory within the Faculty of Rehabilitation Medicine at the University of Alberta. On one day of each week the aerobic portion of the exercise program was performed on a cycle ergometer and involved a 5-minute warm-up with 25-40 minutes of moderate cycling below ventilatory threshold followed by a 5 minute cool down period. On the other two days, subjects performed interval training, with three to eight sets of 2-minute bouts of exercise at a power output achieved at 100% of VO_{2peak} followed by 2 minutes at a power output achieved at 50% of VO_{2peak}.

Exercise intensity was verified by measuring heart rate using Polar heart rate monitors. Interval training was used as it has been shown to have beneficial effects on post exercise lipid metabolism and results in greater weight loss from fat mass than continuous aerobic exercise[32,33]. Heart rate telemetry was used on each subject to ensure training was within target heart rates. Resistance training was performed on large muscle groups tested at 50-65% of maximal strength on the following machines: chest press, leg press, lat pulldown, shoulder press, leg extension, leg curl, tricep pushdown and arm curls..

Assessment of arterial compliance and resting hemodynamics

Arterial compliance was assessed using computerized arterial pulse waveform analysis. This technique involves 30-s recordings of signal averaged arterial pulse waves by applanation tonometry using surface residing pressure transducer on the radial pulse of subjects (Hypertension Diagnostics Inc., Eagan MN). Blood pressure was measured oscillometrically on the opposite arm. The diastolic decay of the waveform was analyzed mathematically and the two components of arterial compliance were calculated based on a modified Windkessel model of circulation: capacitive compliance (large artery), and oscillatory (or reflective) compliance reflecting smaller, more peripherally located arteries and arterioles. This technique has been validated previously[34,35]. A trained technician performed all of the pre and post intervention measurements.

Echocardiographic Measurements.

LV imaging was performed with a commercially available ultrasound instrument (Hewlett Packard, Sonos 5500) with a 3.5 MHz transducer. LV 2-dimensional transthoracic images were obtained from the parasternal short-axis view at the level of the mid-papillary muscles according to American Society of Echocardiography guidelines[36]. All images were obtained by a trained technician. The following measurements were obtained and averaged over three cardiac cycles: posterior wall thickness, ventricular septal wall thickness) and internal cavity dimensions. LV mass was calculated using the Devereux formula. LV mass was indexed for body surface area. LV filling dynamics were assessed with pulsed-wave Doppler of both the transmitral and pulmonary venous flow patterns recorded in the apical four chamber view. Mitral flow

velocities were detected by placing a sample volume between the tips of the mitral valve leaflets during which time the following variables were measured: peak flow velocity in early diastole (E wave) and during atrial contraction (A wave) and their ratio (E/A). Pulmonary venous flow velocities were detected by placing a 3-5 mm sample volume 1-2 cm into the right superior pulmonary vein. The following variables were measured: peak pulmonary venous flow velocity during systole and diastole and atrial contraction.

Blood collection and preparation.

Fasting haematological measurements included: glucose, insulin, HbA_{1c}, high density lipoprotein, low density lipoprotein, triglycerides. All assays were perfomed at the University of Alberta Hospital using standard techniques. In brief, insulin was measured using a Roche Diagnostics Elecsys 2010 System using the sandwich principle. The remaining blood samples were obtained from Roche Hitachi 917 System. Glucose was measured using a hexokinase method. Hemoglobin A_{1C} (HbA_{1c}) was obtained from a turbidimetric method to determine HbA_{1c} and a photometric method to determine hemoglobin. The HbA_{1c} is then reported as a fraction of total hemoglobin. Total cholesterol values were obtained using a cholesterol oxidase method while triglyceride values were obtained using a fully enzymatic colorimetric assay reaction for glycerol following the removal of all serum free glycerol. HDL values were determined from a photometric method after the addition of PEG modified enzymes. LDL is a calculated value: LDL=CHOL-HDL-(TRIG/2.2). The homeostasis model assessment (HOMA index) was used as an estimate of insulin resistance[38].

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 11.0, SPSS, Chicago, IL). A paired sampled T-test was used to compare means for VO_{2peak} and measures of LV function and morphology prior to and following the exercise training intervention. Variables relating to arterial compliance were subsequently used in a repeated measures analysis of covariance using age, systemic vascular resistance, systolic and diastolic blood pressure as covariates. These variables were analyzed as covariates as they have been shown to contribute to changes in vascular compliance. Data are

expressed as the mean ± standard deviation. Univariate ANCOVA was used to test for significant differences. A value of $P < 0.05$ was considered significant.

RESULTS

Of the 16 women initially screened, four women had positive stress tests while two women withdrew midway through the intervention due to personal time commitments. 10 women completed the investigation. Subject characteristics are described in Table 1. There were no additional medications prescribed during the course of the investigation. The ten participants completed an average of 80.3% of the scheduled training sessions. On average, participants exercised for 35-45 minutes per session at an average exercise intensity equivalent to ~77% of heart rate reserve throughout the study.

Hematological data

Fasting blood glucose, insulin and lipid profile are described in Table 2. Ten weeks of exercise did not elicit any significant changes in the fasting blood lipid profile of the participants. Insulin resistance was evident as pre-training HOMA values exceeded 4.0. There was no change in the HOMA index following exercise training.

Peak Exercise Data

Pre-training VO_{2peak} values were 25% below previously published age-predicted maximal oxygen uptake normative values for sedentary women[37]. The subjects achieved an average RER > 1.05 on the initial exercise stress, suggesting a maximal effort during VO_{2peak} testing. After 10 weeks of exercise training, VO_{2peak} increased from 19.9 ± 4.3 to 22.1± 5.0 $ml \cdot kg^{-1} \cdot min^{-1}$ (Figure 1.) and time to exhaustion increased from 14.1 ± 3.2 to 15.8 ± 3.0 min ($p < 0.05$). Maximal heart rate and RER values did change following exercise training, suggesting similar efforts for both tests.

Resting hemodynamics

Large artery compliance increased by ~10% in response to exercise training ($p.< 0.05$) (Figure 2), while small artery compliance remained unchanged. Subsequent to the increase in large artery compliance, a reduction in systemic vascular resistance was also observed ($p.< 0.05$) (Figure 3). When systemic vascular resistance and age were included as covariates, the observed differences in large artery compliance following exercise training were no longer observed. Of the remaining variables obtained from applanation

tonometry the only observable change following exercise training was an increase in stroke volume ($p < 0.05$) (Table 3).

LV function and morphology

LV filling dynamics, estimated from Doppler-derived transmitral and pulmonary venous flow profiles, were not significantly different following 10 weeks of exercise training (Tables 4 & 5). Finally, 10 weeks of exercise training was not associated with significant changes in LV cavity size, wall thickness or mass (Table 6).

DISCUSSION

The major new finding of this investigation is that 10 weeks of exercise training results in an improvement in arterial compliance secondary to an improvement in cardiorespiratory fitness in women with DM-2. Importantly, these observations were made independent of any measurable differences in LV filling dynamics or conventional risk factors for CVD.

Several cross-sectional investigations have demonstrated the beneficial effects of regular physical activity on the age-related decline in arterial compliance[11,13,39]. More importantly, as it relates to this investigation, an acute exercise intervention of 13 weeks has been shown to restore some of the age-related loss in central arterial compliance in previously sedentary men[13]. The finding that exercise attenuates the age-related decline in arterial compliance has also been demonstrated in women[41]. The data presented here data support these observations and extend them to women with DM-2.

Although few investigations have assessed the effects of exercise training on arterial compliance in DM-2, exercise training has been shown to improve endothelial function in persons with DM-2. Eight weeks of training, in type 2 diabetic patients of similar age to those who participated in our investigation (52 ± 2 yrs), resulted in an increase in flow-mediated dilatation from 1.7 to 5.0%[42]. The authors speculated that improvements in vascular function with exercise training may have been mediated through an increased expression of nitric oxide-synthase, thereby enhancing nitric oxide bioavailability. The authors also suggested that exercise-mediated improvements in vascular function in DM-2 may relate to improved metabolic control and the subsequent reduction in advanced glycated end products. Although changes in glycosylated

hemoglobin were not noted in this investigation, a slight but non-significant improvement in insulin sensitivity with exercise training was observed. It is unlikely that changes in metabolic control contributed to changes in vascular function, as changes in HOMA index were not related to changes in vascular function following exercise training. Others have demonstrated that improvements in blood lipid profile increases arterial compliance[43,44], however, lipid profile was unchanged following exercise training in the present investigation. Therefore the underlying mechanisms to explain the exercise-mediated improvements in vascular compliance remain unclear.

Several investigations have demonstrated a significant relationship between LV diastolic filling dynamics and exercise capacity[22,23,25]. Poirier and colleagues[23] demonstrated that in men with DM-2, impaired LV filling dynamics (E/A < 1.0) were associated with a significant reduction in exercise capacity. LV filling dynamics were unchanged following 10 weeks of aerobic and resistance training in older women with DM-2. These findings contrast the work previously described, but support previous investigations that have not demonstrated any change in LV filling dynamics with prolonged endurance training in older women[45] or men[46].

LV filling dynamics have been shown to improve following reductions in LV mass[47]. Since LV mass was unchanged following exercise training, it follows that there we no observed changes in LV filling dynamics. Furthermore, although the ratio of early to late transmitral filling was lower than values previously reported in younger healthy women, the values observed here are slightly higher than those previously reported in males with DM-2[19,48]. Poirier and colleagues[23] defined abnormal LV filling pattern as a ratio of early to late transmitral filling of less than 1.0. In this investigation only 2 of the 10 participants had E/A ratios below this value. Therefore, there may be gender differences with regards to LV diastolic function in persons with DM-2, similar to the gender differences observed in persons with hypertension[21].

Cardiorespiratory fitness has recently been shown to have prognostic impact, independent of several other strong predictors of mortality such as hypertension, smoking, obesity and diabetes[49]. Specifically, in persons with diabetes, an aerobic capacity of < 5 METS (~17.5 $ml \cdot kg^{-1} \cdot min^{-1}$) was associated with a 2.5-fold increase in risk of mortality from a cardiovascular event, compared to diabetics with an aerobic

capacity of >8 METS (~28 $ml \cdot kg^{-1} \cdot min^{-1}$). This is supported by data from Wei and colleagues[27] who demonstrated that VO_{2peak} was an independent predictor of mortality in large cohort of men with DM-2. Based on these findings the 10% increase in VO_{2peak} observed following 10 weeks of exercise training would suggest a decreased risk for overall mortality. Brandenburg and colleagues[50] observed a 26.5% increase (17.7 ± 4.0 vs 22.4 ± 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$) in VO_{2peak} in premenopausal women with DM-2 following 12 weeks of exercise training. Discrepancies between the relative changes in VO_{2peak} observed following training in these investigations are likely due to differences in pre-training cardiovascular fitness.

A few limitations of this investigation need to be addressed. Firstly, we had initially proposed to evaluate postmenopausal women with DM-2. Since, menopausal status was determined from self-report, it is impossible to distinguish between participants in perimenopause from those in true menopause. The perimenopause is a transitional phase of the ovarian cycle during which estrogen levels fluctuate on a less frequent basis than during a normal ovarian cycle. As estrogen has known vascular effects, a limitation of this investigation is that we did not control for estrogen levels in these women. Secondly, the use of a control condition rather than a control group, limits statistical power and prevents us from demonstrating that changes that occurred during the intervention were the direct result of the exercise stimulus. Finally, the non-invasive nature of applanation tonometry does not provide us with information regarding the underlying mechanisms that may explain improvements in peripheral resistance/vascular compliance associated with exercise training in this population.

The role of exercise in the treatment and prevention of with DM-2 is well recognized in clinical practice[51] but remains underutilized because of problems of implementation and patient compliance. Improvements in VO_{2peak} and arterial compliance with exercise training in this population may translate into reductions in the risk for future cardiovascular events and improve functional capacity in these patients. Currently there is a lack of information describing the underlying mechanisms for this exercise-mediated adaptation. The deleterious effects of DM-2 on LV and vascular function have been well established however the effects of exercise training on these variables need to be examined further.

In conclusion, 10 weeks of exercise training improves VO_{2peak} in women with DM-2. In addition to an improvement in functional capacity, exercise training is associated with an increase large artery compliance in this population. Finally, the increase in VO_{2peak} in this population was not associated with a significant change in LV diastolic function.

REFERENCES

1. WB Kannel, DL McGee: Diabetes and cardiovascular risk factors: the Framingham study. Circulation 1979, 59:8-13.

2. SM Haffner, S Lehto, T Ronnemma, K Pyorala, M Laakso: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. N Engl J Med 1998, 339:229–234.

3. NJ Morrish, SL Wang, LK Stevens, JH Fuller, H Keen: Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia 2001, 44 (Suppl 2):S14-S21.

4. GE McVeigh, GM Brennan, GD Johnston, BJ McDermott, LT McGrath, WR Henry, JW Andrews, JR Hayes: Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1992; 35:771-6.

5. HO Steinberg, H Chaker, R Leaming, A Johnson, G Brechtel, AD Baron: Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996, 97:2601-10.

6. JR Cockcroft, DJ Webb, IB Wilkinson: Arterial stiffness, hypertension and diabetes mellitus. J Hum Hypertens. 2000, 14:377–380.

7. DK Arnett, GW Evans, WA Riley: Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol. 1994, 140:669–682.

8. RJ Hodes RJ, EG Lakatta EG, CT McNeil CT: Another modifiable risk factor for cardiovascular disease? some evidence points to arterial stiffness. J Am Geriatr Soc 1995, 43:581–582.

9. V Schachinger, MB Britten, AM Zeiher: Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation. 2000, 101: 1899–1906.

10. TM Rywik, MR Blackman, AR Yataco, PV Vaitkevicius, RC Zink, EH Cottrell, JG Wright, LI Katzel, JL Fleg: Enhanced endothelial vasoreactivity in endurance-trained older men. J Appl Physiol, 1999;87:2136-42.

11. H Tanaka, FA Dinenno, KD Monahan, CM Clevenger, CA DeSouza, DR Seals: Aging, habitual exercise, and dynamic arterial compliance. Circulation 2000;102:1270-5.

12. MR Rinder, RJ Spina, AA Ehsani. Enhanced endothelium-dependent vasodilation in older endurance-trained men. J Appl Physiol. 2000;88:761-6.

13. KD Monahan, FA Dinenno DR Seals, JR Halliwill: Smaller age-associated reductions in leg venous compliance in endurance exercise-trained men. Am J Physiol Heart Circ Physiol. 2001;281:H1267-73.

14. JG Regensteiner, J Sippel, ET McFarling, EE Wolfel, WR Hiatt: Effects of non-insulin-dependent diabetes on oxygen consumption during treadmill exercise. Med Sci Sports Exerc. 1995;27:875-81.

15. WB Kannel, M Hjortland, WP Castelli. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 1974;34:29-34.

16. FS Fein, EH Sonnenblick. Diabetic cardiomyopathy. Prog Cardiovasc Dis. 1985; 27(4):255-70.

17. RB Devereux, MJ Roman, M Paranicas, MJ O'Grady, ET Lee, TK Welty, RR Fabsitz, D Robbins, ER Rhoades, BV Howard: Impact of diabetes on cardiac structure and function: the strong heart study. Circulation. 2000;101:2271-6.

18. H Taegtmeyer, P McNulty, ME Young: Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation. 2002;105:1727-33.

19. P Poirier, P Bogaty, C Garneau, L Marois JG Dumesnil: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care. 2001; 24:5-10.

20. M Zabalgoitia, MF Ismaeil, L Anderson, FA Maklady: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am J Cardiol. 2001; 87:320-3.

21. JN Bella, V Palmieri, MJ Roman, JE Liu, TK Welty, ET Lee, RR Fabsitz, BV Howard, RB Devereux: Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation. 2002;105(16):1928-33.

22. JJ Vanoverschelde, B Essamri, R Vanbutsele, A d'Hondt, JR Cosyns, JR Detry, JA Melin: Contribution of left ventricular diastolic function to exercise capacity in normal subjects. J Appl Physiol. 1993; 74(5):2225-33.

23. P Poirier, C Garneau, P Bogaty, A Nadeau, L Marois, C Brochu, C Gingras, C Fortin J Jobin, JG Dumesnil: Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol. 2000; 85(4):473-7.

24. GF Fletcher, GJ Balady, EA Amsterdam, B Chaitman, R Eckel, J Fleg, VF Froelicher, AS Leon, IL Pina, R Rodney, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation. 2001;104(14):1694-740.

25. WC Levy, MD Cerqueira, AB Abrass, RS Schwartz, JR Stratton: Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. Circulation. 1993; 88(1):116-26.

26. American College of Sports Medicine and American Diabetes Association joint position statement. Diabetes mellitus and exercise. Med Sci Sports Exerc. 1997, 29(12):i-vi.

27. M Wei, LW Gibbons, JB Kampert, MZ Nichaman, SN Blair: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 2000;132(8):605-11.

28. WB Kannel, PW Wilson. Risk factors that attenuate the female coronary disease advantage. Arch Intern Med. 1995;155(1):57-61.

29. EL Barrett-Connor, BA Cohn, DL Wingard, SL Edelstein. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991;265(5):627-31.

30. BV Howard, LD Cowan, O Go, TK Welty, DC Robbins, ET Lee: Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. Diabetes Care. 1998;21:1258-65.

31. H Tanaka, KD Monahan, DR Seals: Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37:153-6.

32. A Tremblay, JA Simoneau, C Bouchard: Impact of exercise intensity on body fatness and skeletal muscle metabolism. Metabolism. 1994;43:814-8.

33. M Yoshioka, E Doucet, S St-Pierre, N Almeras, D Richard, A Labrie, JP Despres, C Bouchard, A Tremblay: Impact of high-intensity exercise on energy expenditure, lipid oxidation and body fatness. Int J Obes Relat Metab Disord. 2001;25(3):332-9.

34. E-R Rietzschel, E Boeykens ML, De Buyzere, DA Duprez, DL Clement: A Comparison Between Systolic and Diastolic Pulse Contour Analysis in the Evaluation of Arterial Stiffness. Hypertension. 2001 37: e15-22.

35. CH Chen, E Nevo, B Fetics, PH Pak, FC Yin, WL Maughan, DA Kass: Estimation of central aortic pressure waveform by mathematical transformation of

radial tonometry pressure. Validation of generalized transfer function. Circulation. 1997;95:1827-36.

36. DJ Sahn, A DeMaria, J Kisslo, A Weyman: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 1978;58:1072-83.

37. MD Fitzgerald, H Tanaka, ZV Tran, DR Seals: Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. J Appl Physiol. 1997;83:160-5.

38. DR Matthews, JP Hosker, AS Rudenski, BA Naylor, DF Treacher, RC Turner: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9.

39. CA DeSouza, LF Shapiro, CM Clevenger, FA Dinenno, KD Monahan, H Tanaka, DR Seals: Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. Circulation. 2000, 102:1351-7.

40. V Salomaa, W Riley, JD Kark, C Nardo, AR Folsom; Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation. 1995, 91:1432-43.

41. H Tanaka, CA DeSouza, DR Seals: Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler Thromb Vasc Biol. 1998;18:127-32.

42. A Maiorana, G O'Driscoll, C Cheetham, L Dembo, K Stanton, C Goodman, R Taylor, D Green: The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001, 38:860-6.

43. H Shige, A Dart, P Nestel: Simvastatin improves arterial compliance in the lower limb but not in the aorta. Atherosclerosis. 2001;155:245-50.

44. KE Ferrier, MH Muhlmann, JP Baguet, JD Cameron, GL Jennings, AM Dart, BA Kingwell: Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol. 2002;39:1020-5.

45. RJ Spina, S Rashid, VG Davila-Roman, AA Ehsani: Adaptations in beta-adrenergic cardiovascular responses to training in older women. J Appl Physiol. 2000;89:2300-5.

46. FL Fleg, EP Shapiro, F O'Connor, J Taube, AP Goldberg, EG Lakatta: Left ventricular diastolic filling performance in older male athletes. JAMA. 1995, 273:1371-5.

47. K Wachtell, JN Bella, J Rokkedal, V Palmieri, V Papademetriou, B Dahlof, T Aalto, E Gerdts, RB Devereux: Change in diastolic left ventricular filling after one year of antihypertensive treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. Circulation. 2002, 105:1071-6.

48. JE Liu, V Palmieri, MJ Roman, JN Bella, R Fabsitz, BV Howard, TK Welty, ET Lee, RB Devereux: The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol. 2001, 37:1943-9

49. J Myers, M Prakash, V Froelicher, D Do, A Partington, JE Atwood: Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002, 346:793-801.

50. SL Brandenburg, JE Reusch, TA Bauer, BW Jeffers, WR Hiatt, JG Regensteiner: Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care. 1999, 22:1640-6.

51. J Tuomilehto, J Lindstrom, JG Eriksson, TT Valle, H Hamalainen, P Ilanne-Parikka, S Keinanen-Kiukaanniemi, M Laakso, A Louheranta, M Rastas et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001, 344:1343-50.

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Table 1. Subject characteristics (n=10)

Variable	Pre Training	Post Training
Age (yrs)	56 ± 4	---
Weight (kg)	95.4 ± 12.1	94.1 ± 13.1
BMI (kg/m^2)	35.9 ± 4.2	35.3 ± 5.2

Table 2. Changes in hematological values with training (n=10)

Variable	Pre-Training	Post-Training
HbA_{1c} (%)	6.7 ± 1.1	6.6 ± 0.9
TC (mmol/L)	5.4 ± 1.5	5.5 ± 1.6
HDL (mmol/L)	1.28 ± 0.2	1.30 ± 0.3
LDL (mmol/L)	2.9 ± 1.0	2.8 ± 0.8
TG (mmol/L)	2.8 ± 2.1	2.8 ± 1.8
Glucose (mmol/L)	7.6 ± 1.8	8.1 ± 1.9
Insulin (mmol/L)	14.1 ± 6.6	13.2 ± 6.6
HOMA	5.1 ± 2.7	4.6 ± 2.9

TC = Total cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein; TG = triglyceride

Table 3. Changes in resting cardiovascular hemodynamics with exercise training (n=10)

Variable	Pre-Training	Post-Training
Heart rate	75 ± 12	72 ± 14
SBP (mmHg)	143 ± 15	137 ± 15
DBP (mmHg)	81 ± 6	77 ± 12
LAC (mL/mmHg)	1.03 ± 0.46	1.22 ± 0.41*
SAC (mL/mmHg)	0.047 ± 0.035	0.035 ± 0.013
LAC ** **(mL/mmHg)**	1.07 ± 0.13	1.31 ± 0.16*
SV (mL)	65 ± 16	74 ± 16*
C.I. (L/m^2)	2.45 ± 0.24	2.59 ± 0.19
Qc (L)	4.9 ± 0.6	5.1 ± 0.5
SVR ($dynes \cdot sec \cdot cm^{-5}$)	1800 ± 418	1587 ± 210*

SBP = systolic blood pressure; DBP = diastolic blood pressure; LAC = large artery compliance; SAC = small artery compliance; SV = stroke volume; C.I. = cardiac index; Qc = cardiac output; SVR = systemic vascular resistance

Table 4. Changes in LV transmitral filling dynamics with exercise training (n=10)

Variable	Pre-Training	Post-Training
E (cm/s)	87 ± 8	83 ± 13
A (cm/s)	90 ± 23	84 ± 16
E/A ratio	1.03 ± 0.29	1.01 ± 0.21
Deceleration time (ms)	231.3 ± 24.0	237.0 ± 37.8

E= early transmitral filling; A = transmitral filling during atrial contraction
E/A ratio = ratio of early to late diastolic transmitral filling fractions

Table 5. Changes in pulmonary venous flow rates with exercise training (n=10)

Variable	Pre-Training	Post-Training
PVs	61.5 ± 7.7	65.6 ± 11.4
PVd	42.2 ± 9.6	48.9 ± 12.5
PVs:PVd	1.49 ± 0.17	1.38 ± 0.23
Pva	28.5 ± 7.7	29.8 ± 5.2
Pva Duration	121.8 ± 13.2	131.3 ± 18.8
Pvad-Mad	-60.25 ± 52.9	-42.9 ± 32.2

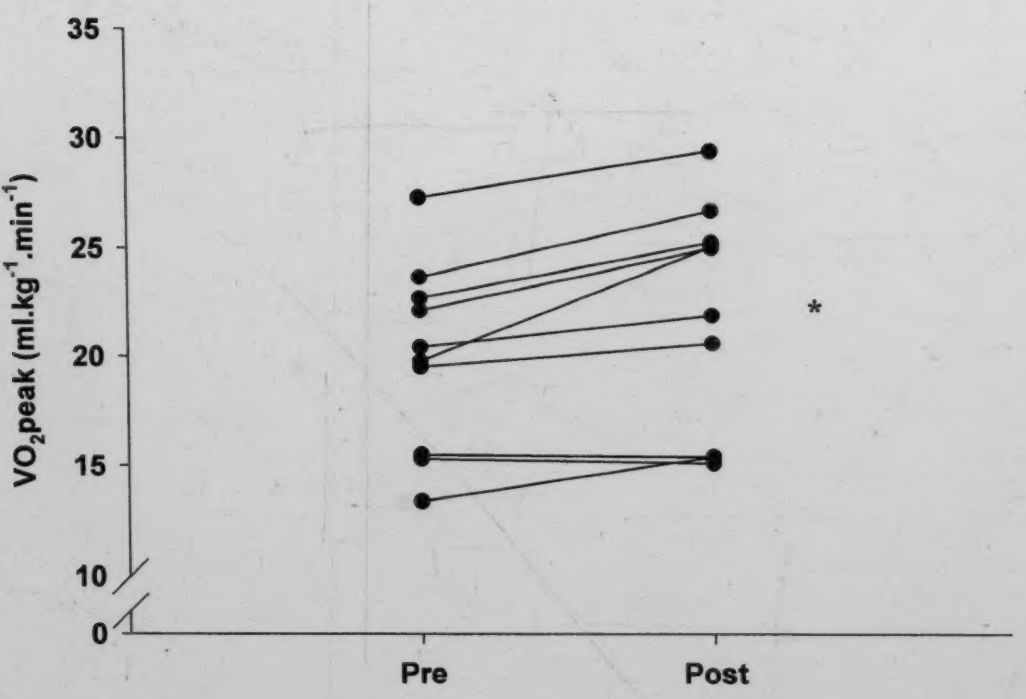
PV = pulmonary venous flow, s = ventricular systole, d = ventricular diastole, a – atrial contraction, Pvad – Mad = pulmonary venous flow duration during atrial systole – transmitral flow duration during atrial systole

Table 6. Changes in LV morphology with exercise training (n = 10)

Variable	Pre-Training	Post-Training
IVS (mm)	10.4 ± 2.3	11.0 ± 1.1
PWT (mm)	10.3 ± 2.4	10.9 ± 0.9
LVID (mm)	51.1 ± 6.9	48.6 ± 5.5
LVM (g)	195 ± 67	200 ± 41
LVMI (g/m^2)	96.7 ± 29.6	119 ± 23.5
RWT	0.41 ± 0.11	0.45 ± 0.07

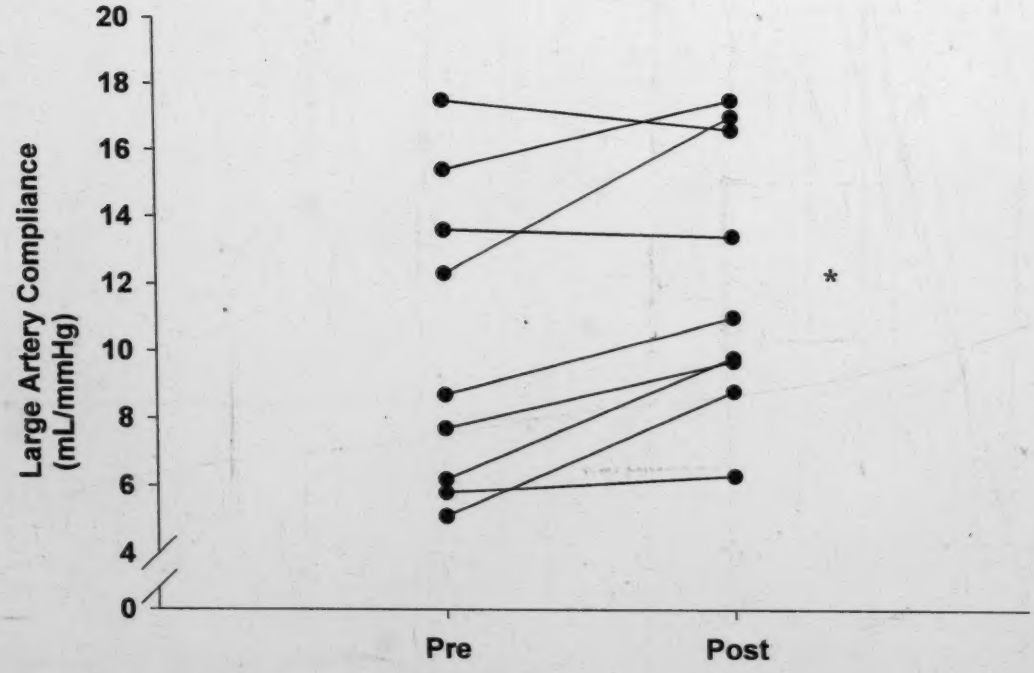
IVS = interventricular septum, PWT = posterior wall thickness, LVID = left ventricular interval diameter at end-diastole, LVM = left ventricular mass, LVMI = LVM index for body surface area, RWT = relative wall thickness.

Figure 1.



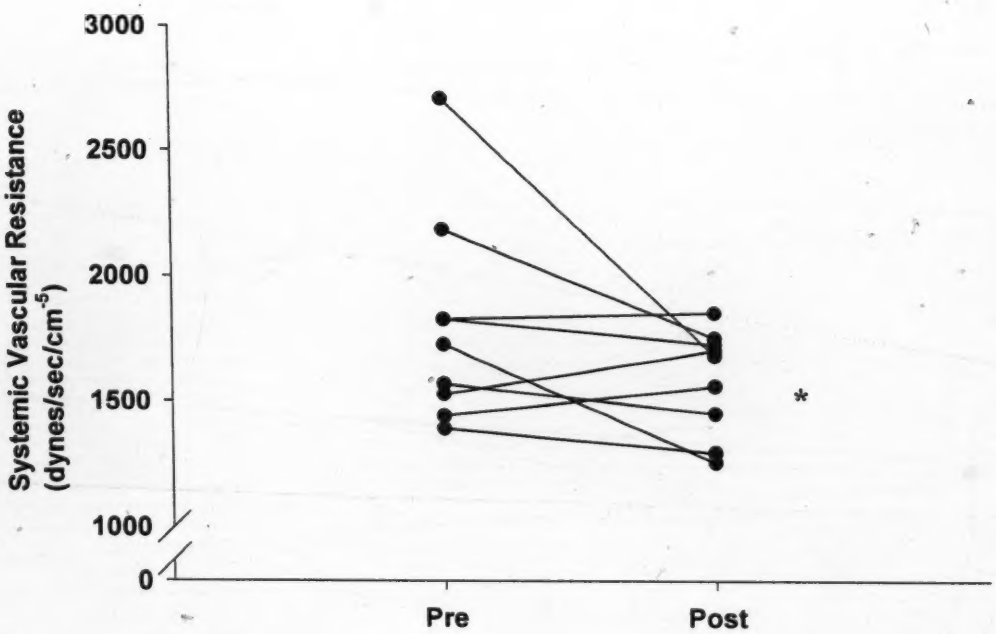
* = $p < 0.05$ vs Pre

Figure 2



* $p < 0.05$ vs pre

Figure 3.



* = $p < 0.05$ vs Pre

Chapter IV.
Study III

The Effects of Exercise Training on Left Ventricular and Vascular Function in Women with Type II Diabetes Mellitus

INTRODUCTION

Type 2 diabetes (DM-2) is associated with an increased risk for the development of cardiovascular disease[1] (CVD) and heart failure[2]. Furthermore, macrovascular disease accounts for up to 80% of all deaths in this population[3,4]. The increased CVD-related mortality and morbidity associated with DM-2 may be attributed to the common presence of synergistic co-morbidities such as hypertension, dyslipidemia and obesity. However, recent evidence suggests that cardiac[5] and vascular[6,7] maladaptations, such as impaired left ventricular (LV) filling dynamics, increased arterial stiffness[6] and endothelial dysfunction[7] may also contribute to these observations.

Exercise training has been shown to attenuate age-associated declines in LV filling dynamics[8] and arterial compliance[9,10] in older healthy individuals, implying that cardiovascular maladaptations associated with aging may be more a function of physical inactivity than of senescence. Several lines of evidence suggest that similar cardiovascular adaptations to exercise training may be achieved in persons with DM-2[11-13]. Specifically, remarkably similar improvements in glucose transport[11], cardiorespiratory fitness[12,13] and oxygen uptake kinetics[13] have been documented following exercise training between individuals with DM-2 and age-matched healthy controls. Surprisingly, the cardiovascular adaptations to explain enhanced cardiorespiratory fitness or oxygen uptake kinetics following exercise training in persons with DM-2 have yet to be described. Moreover, high cardiorespiratory fitness has been shown to be cardioprotective in healthy aged and persons with DM-2, independent of conventional risk factors for CVD (14). The mechanisms for this cardioprotection have yet to be elucidated. However, it is possible that they are mediated through enhanced LV diastolic filling properties, reduced arterial stiffness and/or endothelial dysfunction.

The primary purpose of this investigation was to examine the effects of exercise training on known correlates of cardiorespiratory fitness, mainly LV filling dynamics, arterial compliance and endothelial function in women with DM-2. Women were studied in this investigation as current literature suggests that women with DM-2 are at a greater risk for the development of CVD compared to men with DM-2[15,16]. We hypothesized that a 10-week exercise training intervention in women with DM-2 would improve

cardiorespiratory fitness subsequent to improvements in LV diastolic filling properties, arterial compliance and endothelial function.

METHODS

Subjects

A total of 14 postmenopausal women (58 ± 5 yrs) with clinically documented DM-2, free from diabetic complications, were screened for underlying coronary artery disease with resting and maximal exercise electrocardiograms. Presence of DM-2 was documented by chart review to confirm the type of diabetes. Exclusion criteria for this investigation included: evidence of ischemic heart disease by history or by resting or exercise electrocardiogram; angina or any other cardiac symptoms potentially limiting exercise capacity; presence of musculoskeletal or peripheral vascular abnormalities that would limit exercise capacity. Four women were excluded based on these criteria. Informed consent was obtained from all subjects prior to the investigation and the Research Ethics Review Board at the University of Alberta approved the study protocol.

Study protocol

Prior to exercise training, subjects were evaluated over the course of two separate visits. Initially, participants reported to the University of Alberta Hospital, Division of Cardiology for a history and physical examination as well as a resting and exercise ECG. A graded exercise test was performed on an electronically braked cycle ergometer to determine cardiorespiratory fitness. On the second visit, subjects reported to the Metabolic Unit between 7 and 9 a.m. following an overnight fast for blood work, applanation tonometry and resting echocardiograms. Following baseline testing, participants were assigned to either control (CT; n=7) or exercise training (ET; n=7) groups. All measurements were repeated following the 10-week intervention period.

Graded exercise test to exhaustion

Oxygen consumption, carbon dioxide production and minute ventilation were sampled every five seconds at rest and during exercise using a Parvo Medics TrueMax 2400 Metabolic Cart (Parvo Medics, East Sandy, UT). Exercise was performed on a

cyucle ergometer, beginning at a workload of 30 watts and increasing by 15 watts every two minutes until volitional exhaustion. Heart rate (12 lead ECG), blood pressure (auscultation) and a rating of perceived exertion (Borg scale) was determined at the end of each stage. Subjects were encouraged to continue exercising until respiratory exchange ratio exceeded 1.15 and/or heart rate was within 5 beats of age-predicted maximum.

Cardiorespiratory fitness ($\dot{V}O_{2peak}$) was considered the peak rate of oxygen consumption during the last 60 seconds of the graded exercise test. The heart rate response to graded exercise was used to prescribe exercise intensity during the exercise intervention.

Assessment of arterial compliance and resting hemodynamics

Arterial compliance was assessed using computerized arterial pulse waveform analysis. This technique involves 30-s recordings of signal-averaged arterial pulse waves by applanation tonometry using a surface residing pressure transducer on the radial artery (Hypertension Diagnostics Inc., Eagan MN). The diastolic decay of the waveform was analyzed mathematically. Two components of arterial compliance were calculated based on a modified Windkessel model of circulation: capacitive compliance (large artery), and oscillatory (or reflective) compliance[17]. This technique has been validated previously[18].

Endothelial Function

Endothelial function was measured using a previously validated technique described in detail elsewhere[19]. In brief, patients were supine for 20 minutes before the first ultrasound scan was recorded. Brachial artery diameter, mean arterial pressure and heart rate were measured at rest and following flow-mediated dilatation induced by reactive hyperemia and sublinguinal administration of glyceryl trinitrate.

The monitored, non-dominant arm was positioned at 80° of elbow flexion with the distal forearm supinated and immobilized. A continuous 3-lead ECG was used to measure heart rate and determine the specific points of the cardiac cycle. A 12-MHz multifrequency linear array transducer attached to a high resolution ultrasound machine (Sonos 5500, Hewlett Packard) was used to visualize the artery in the distal third of the upper arm. A sphygmomanometer cuff was placed proximal to the transducer and inflated to a suprasystolic pressure as determined by radial palpation for a duration of 5

minutes. One minute following cuff deflation the brachial artery diameter was measured using ultrasonic B-mode imaging. Dilatation of the brachial artery was stimulated by reactive hyperemia, and was used to determine endothelium-dependent vasodilation. Images were obtained at 1 and 3 minutes following cuff deflation.

When artery diameter returned to baseline values (~15 minutes) a second baseline scan was recorded. This was followed by a sublinguinal administration of GTN at a dose of 400μg that provided an index of endothelium independent vasodilation. B-mode images were again taken at one and three minutes following GTN administration. All images were acquired by a trained technician, on VHS tapes and digitally recorded.

Echocardiographic Measurements.

Imaging of the LV was performed as previously described[20-22]. In brief, all images were captured using a commercially available ultrasound instrument (Hewlett Packard, Sonos 5500) with a 3.5 MHz transducer. Two-dimensional transthoracic images of the LV were obtained from the parasternal short-axis view at the level of the mid-papillary muscles according to American Society of Echocardiography guidelines[20]. LV morphology was estimated from previously published formulas[21]. LV diastolic filling dynamics were assessed using pulsed-wave Doppler analysis of transmitral and pulmonary venous flow patterns recorded in the apical four chamber view[22]. All echocardiographic images were averaged over three cardiac cycles.

Blood collection and analysis.

Blood was drawn in the fasted state prior to ultrasound imaging. Fasting haematological measurements included: glucose, insulin, hemoglobin A_{1c}, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides. All assays were perfomed at the University of Alberta Hospital using standard techniques. Insulin was measured using a Roche Diagnostics Elecsys 2010 System using the sandwich principle. Glucose was measured using a hexokinase method. Total cholesterol values were obtained using a cholesterol oxidase method while triglyceride values were obtained using a fully enzymatic colorimetric assay reaction for glycerol following the removal of all serum free glycerol. HDL values were determined from a photometric method after

the addition of PEG modified enzymes. The ratio of triglycerides to HDL was used as an estimate of LDL particle size[23]. The homeostasis model assessment (HOMA index) was used as an estimate of insulin sensitivity[24].

Exercise Intervention

The 10-week exercise intervention consisted of three supervised exercise sessions per week and included a combination of aerobic and resistance training. The aerobic component of the exercise program was performed on a cycle ergometer and involved both continuous and interval training. Continuous exercise training was performed twice a week and consisted of a 5-10 minute warm-up with 30-55 minutes of moderate cycling below ventilatory threshold followed by a 5-10 minute cool down period. Interval training was performed once a week and consisted of repeated 2-minute bouts of cycling alternating between 50% and 100% of peak power output achieved during the maximal exercise test. Exercise intensities were determined by heart rate telemetry. Resistance training was performed on 10-15 repititions at 50-65% of maximal strength on the following machines: chest press, leg press, lat pulldown, shoulder press, leg extension, leg curl, tricep pushdown and arm curls. Control subjects continued activities of daily living for 10 weeks. Individuals in this investigation were treated for diabetes through diet and exercise or oral hypoglycemic agents, while no participants were on insulin therapy.

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 11.0, SPSS, Chicago, IL). A two-way repeated measures ANOVA was used to compare differences in changes in conventional and novel risk factors for CVD between the groups following the intervention time period. A p value of < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics of both groups are provided in Table 1. At baseline, there were no significant differences in conventional risk factors for CVD, such as age, body

mass index, systolic blood pressure, lipid profile or fasting insulin or glucose levels between the ET and CT groups. Menopausal status was determined from self report and no women were taking hormone replacement therapy. No differences in VO_{2peak}, maximal heart rate and respiratory exchange ratio were observed between the ET and CT groups at baseline suggesting similar efforts during baseline exercise testing. Pre-training VO_{2peak} values in both groups were ~20% (20.9 ± 3.8 vs 23.8 ± 1.9 $ml \cdot kg^{-1} \cdot min^{-1}$) below previously published age-predicted norms for sedentary women[25].

Exercise Training Data

Resting hemodynamics prior to and following the exercise intervention are provided in Table 2. Participants in the ET group performed 92 ± 3% of the exercise sessions. The subjects achieved an average respiratory exchange ratio >1.05 at peak exercise, suggesting a maximal effort during VO_{2peak} testing. After 10 weeks of exercise training, VO_{2peak} increased by approximately 15% (18.8 ± 3.5 to 21.6 ± 6.3 $ml \cdot kg^{-1} \cdot min^{-1}$; $p < 0.05$) while time to exhaustion increased by 10% (15.0 ± 3.2 to 16.6 ± 3.0 min; $p<0.05$). Maximal heart rate and respiratory exchange ratio values at follow-up testing were similar to the baseline values, suggesting similar effort for both tests. Cardiorespiratory fitness was not assessed in the CT group during follow-up testing.

Fasting blood glucose, insulin and lipid profile before and after the 10-week intervention period are presented in Table 1. In the present study 10 weeks of exercise training did not elicit appreciable changes in the fasting blood lipid profile or hemoglobin A_{1c}. Similarly hematological variables were not significantly different in the CT group following the intervention time period. The HOMA index of insulin sensitivity decreased by ~17% in the ET while it did not change in CT. However these changes did not reach statistical significance.

LV filling dynamics, estimated from Doppler-derived transmitral and pulmonary venous flow profiles, were not significantly different following the intervention time period in either group. In the ET group, large artery compliance increased by ~16% in response to exercise training ($p< 0.05$), while small artery compliance remained unchanged. Large and small artery compliance were unchanged in the CT group.

Endothelial-dependent dilatation increased significantly in the ET group ($p < 0.05$) and was unchanged in the CT group (Figure 1).

DISCUSSION

The major novel finding of this investigation is that 10 weeks of exercise training elicited an increase in arterial compliance and endothelial-dependent diltatation, secondary to an exercise training –mediated improvement in cardiorespiratory fitness in women with DM-2. These cardiovascular adaptations were present despite any appreciable change in LV filling dynamics or conventional CVD risk factors, such as blood pressure, lipid profile or insulin sensitivity.

Significant negative correlations have been observed between cardiorespiratory fitness and arterial stiffness[9,10,26], suggesting that exercise training may modulate central arterial compliance. More importantly, regular physical activity has been shown to attenuate the age-related decline in arterial compliance in healthy older men and women[9,10,26]. Specifically, arterial compliance was 20-35% higher in older well-trained masters athletes (13-26% greater VO_{2peak} values) compared to their sedentary peers[10,26]. Furthermore, a 16-week home-based exercise intervention elicited a 20% reduction in arterial stiffness in previously sedentary older men[10]. The data presented here support these observations and extend them to women with DM-2. More importantly, similar to previous investigations[9,25], arterial compliance increased without any concomitant change in mean arterial blood pressure.

Increased arterial stiffness in persons with DM-2 may be attributed to insulin resistance, oxidative stress and the development of advanced glycated end-products[27]. Interestingly, treatment of older individuals with a novel advanced glycated end-product crosslink breaker led to a reduction in arterial stiffness[28]. As no changes in glycosylated hemoglobin were noted following a 10-week exercise intervention, the improvement in arterial compliance were not likely a function of a reduction in advanced glycated end-products. Similarly, although others have demonstrated improvements in arterial compliance following lipid lowering therapy[29,30], no appreciable changes in total cholesterol, LDL, HDL or triglycerides were observed following exercise training in this investigation. Although insulin sensitivity (HOMA index) increased slightly with

exercise training it is unlikely that enhanced metabolic control contributed to the improvement in arterial compliance as changes in the HOMA index were unrelated to changes in arterial compliance following an exercise intervention. Therefore, the observed improvement arterial compliance with exercise training in women with DM-2 in this investigation cannot be attributed to changes in lipid or glucose metabolism.

Improved endothelium-mediated vasodilatation or a reduction in intima-media wall thickness[31] may explain enhanced arterial compliance with exercise training in older individuals. Exercise training-mediated improvements in endothelium-dependent dilatation have recently been documented in persons with DM-2[32]. Specifically, Maiorana and colleages[8] showed that eight weeks of aerobic and resistance exercise training increased flow-mediated dilatation from 1.7% to 5.0%, in middle-aged patients with DM-2[32]. The data presented here confirm and extend these findings to women with DM-2. In addition these data suggest that improvements in arterial stiffness with exercise training in women with DM-2 may be related to an enhanced endothelial-dependent dilatation.

Similar to the relationship observed between cardiorespiratory fitness and arterial compliance, a positive association between LV filling and exercise capacity has been observed in several populations[33-36], implying that exercise training may modulate LV diastolic function. Furthermore, some[8, 37-42] but not all[43] cross-sectional and intervention studies have demonstrated that age-related reductions in LV filling dynamics may be attenuated with endurance exercise training. Interestingly, Poirier and colleagues[44] have demonstrated a relationship between cardiorespiratory fitness and LV filling dynamics in normotensive men with DM-2. Contrary to these findings, LV transmitral or pulmonary venous flow profiles remained unchanged following exercise training, despite a significant improvement in $VO_{2peak\ k}$ in women with DM-2.

Several differences between this investigation and that of others may explain discrepant findings. First, the training stimulus employed in this investigation may not have been of sufficient duration (10 weeks) or frequency (three days/week) to elicit appreciable changes in the structure or cellular properties of the LV that could be measured using Doppler-derived transmitral flow patterns[38]. Secondly, gender differences in the LV adaptation to exercise training may explain our results[39,44]. This

explanation is in concordance with exercise-induced improvements in LV contractile function and filling dynamics reported in older men, but not older women, following extensive endurance training[40, 45].

An average improvement in cardiorespiratory fitness following short-term (<16 weeks) exercise training interventions in persons with DM-2 is approximately 15%. Studies of this nature have been comprised of mainly men or mixed cohorts. Therefore, the magnitude of change in cardiorespiratory fitness following exercise training in women with DM-2 is, for the most part, poorly documented. Brandenburg *et al.*[13] observed a 26.5% increase (17.7 ± 4.0 vs 22.4 ± 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$) in VO_{2peak} in premenopausal women with DM-2 following 12 weeks of aerobic exercise training similar to the intervention used in this investigation. Discrepancies between the relative changes in VO_{2peak} observed following training between our investigation and that of Brandenburg *et al*[13], are likely due to differences in pre-training cardiovascular fitness. Since we did not measure cardiac output or arterio-venous oxygen difference in this investigation, we cannot speculate as to the mechanisms which could explain the increased rate of oxygen consumption following exercise training observed in this investigation.

The findings presented here results have several clinical implications. As up to 80% of all deaths in persons with DM-2 may be attributed to some type of cardiovascular disorder[3], interventions that ameliorate CVD-risk are paramount in the treatment of these patients. Increased arterial stiffness and endothelial dysfunction have been identified as independent modifiable CVD risk factors[46,47]. The results of this study demonstrate that a brief exercise intervention in women with DM-2 enhances arterial compliance and endothelial-dependent dilatation, which could be interpreted as a reduction in the risk for CVD morbidity and mortality. More importantly, these adaptations occurred despite little or no change in blood pressure, cholesterol profile or insulin sensitivity. Therefore, the non-invasive determination of arterial compliance and endothelial-dependent dilatation, in addition to conventional markers, may provide important additional information in the assessment of CVD risk and/or treatment efficacy in individuals with DM-2[46,47]. Finally, low cardiorespiratory fitness in men with DM-2 is associated with an increased mortality risk, independent of conventional CVD risk

factors[13]. Therefore, increased cardiorespiratory fitness in women with DM-2 observed following an exercise intervention might reduce the risk for CVD-related morbidity and mortality. These data lend support to the need for exercise training in the prevention and treatment of CVD-related morbidity in persons with DM-2.

A few limitations of this investigation need to be addressed. Firstly, although demographic data were similar between both groups at baseline, the ET group had significantly greater large arterial compliance at the baseline compared to the CT group (Table 2). Although it is possible that these differences may have affected our results, we would expect the ET group to have less adaptive reserve relative to the CT group with lower arterial compliance at baseline. It is doubtful that these baseline differences contributed the observed changes in arterial compliance following exercise training. Secondly, it is possible that group differences in arterial compliance were a function of a menopausal status. As we relied upon self-report of menopausal status, we are unable to distinguish between participants in perimenopause from those in true menopause. The perimenopause is a transitional phase of the ovarian cycle during which estrogen levels fluctuate on a less frequent basis than during a normal ovarian cycle. As estrogen has known vascular actions[48], it is possible that the baseline differences in larger artery compliance were a function of differences in estrogen status between the two groups.

Finally, we did not assess LV or arterial function during physiological stress such as exercise or β-adrenergic stimulation. Therefore we are unable to determine whether exercise training elicited improvements in inotropic or lusitropic reserve. Several investigations have demonstrated impaired inotropic responsiveness in both elderly[49] and individuals with DM-2[50,51]. Furthermore, improved inotropic reserve with endurance exercise training has been documented in healthy older men[52]. Although we cannot eliminate the possibility that an exercise-induced improvement in cardiorespiratory fitness was a function of enhanced LV inotropic reserve, to our knowledge, this adaptation is limited to males[45,52].

In conclusion, 10 weeks of exercise training improves cardiorespiratory fitness, large artery compliance and endothelial-dependent dilatation in women with DM-2. These adaptations were achieved without any significant changes in LV filling dynamics

or conventional CVD risk factors, such as blood pressure, lipid profile or insulin sensitivity.

REFERENCES

1. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. Circulation. 59:8-13, 1979.

2. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. Am J Cardiol. 34:29-34, 1974.

3. Haffner SM, Lehto S, Ronnemma T, Pyorala T, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. N Engl J Med. 339:229–234, 1998.

4. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 44 (Suppl 2):S14-S21, 2001.

5. Taegtmeyer H, McNulty P, Young ME: Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. Circulation. 105:1727-33, 2002.

6. McVeigh G, Brennan G, Hayes R, Cohn J, Finkelstein S, Johnston D. Vascular abnormalities in non-insulin-dependent diabetes mellitus identified by arterial waveform analysis. Am J Med. 95:424-30, 1993

7. McVeigh GE, Brennan GM, Johnston GD, McDermott BJ, McGrath LT, Henry WR, Andrews JW, Hayes JR. Impaired endothelium-dependent and independent vasodilation in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia.;35:771-6, 1992

8. Levy WC, Cerqueira MD, Abrass IB, Schwartz RS, Stratton JR. Endurance exercise training augments diastolic filling at rest and during exercise in healthy young and older men. Circulation. 88:116-26, 1993

9. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation. 88:1456-62, 1993.

10. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation. 102:1270-5, 2000.

11. Kennedy JW, Hirshman MF, Gervino EV et al. Acute exercise induces GLUT4 translocation in skeletal muscle of normal human subjects and subjects with type 2 diabetes. Diabetes. 48:1192-7, 1999.

12. Segal KR, Edano A, Abalos A, Albu J, Blando L, Tomas MB, Pi-Sunyer FX. Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. J Appl Physiol. 71:2402-11, 1991.

13. Brandenburg SL, Reusch JE, Bauer TA, Jeffers BW, Hiatt WR, Regensteiner JG. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care. 22:1640-6, 1999

14. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 132:605-11, 2000.

15. Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. Arch Intern Med.155:57-61, 1995

16. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 265:627-31, 1991.

17. Rietzschel ER, Boeykens E, De Buyzere ML, Duprez DA, Clement DL. A comparison between systolic and diastolic pulse contour analysis in the evaluation of arterial stiffness. Hypertension. 37:E15-22, 2001.

18. Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. Circulation. 95:1827-36, 1997.

19. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol.39:257-65, 2002.

20. Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation. 58:1072-83, 1978.

21. Reichek N, Devereux RB. Reliable estimation of peak left ventricular systolic pressure by M-mode echographic-determined end-diastolic relative wall thickness: identification of severe valvular aortic stenosis in adult patients. Am Heart J 103:202-3, 1982.

22. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG . Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care. 24:5-10, 2001.

23. Boizel R, Benhamou PY, Lardy B, Laporte F, Foulon T, Halimi S. Ratio of triglycerides to HDL cholesterol is an indicator of LDL particle size in patients with type 2 diabetes and normal HDL cholesterol levels. Diabetes Care. 23:1679-85, 2000.

24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 28:412-9, 1985.

25. Fitzgerald MD, Tanaka H, Tran ZV, Seals DR. Age-related declines in maximal aerobic capacity in regularly exercising vs. sedentary women: a meta-analysis. J Appl Physiol. 83(1):160-5, 1997.

26. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler Thromb Vasc Biol. 18:127-32, 1998.

27. Eckel RH, Wassef M, Chait A, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group II: pathogenesis of atherosclerosis in diabetes. Circulation. 105:e138-43, 2002.

28. Kass DA, Shapiro EP, Kawaguchi M et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation.104:1464-70, 2001.

29. Shige H, Dart A, Nestel P. Simvastatin improves arterial compliance in the lower limb but not in the aorta. Atherosclerosis. 155:245-50, 2001.

30. Ferrier KE, Muhlmann MH et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol. 39:1020-5, 2002.

31. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation. 107:139-46, 2003.

32. Maiorana A, O'Driscoll G, Cheetham C et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 38:860-6, 2001.

33. Lapu-Bula R, Robert A, De Kock M et al. Relation of exercise capacity to left ventricular systolic function and diastolic filling in idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol. 83:728-34, 1999.

34. Sakate Y, Yoshiyama M, Hirata K et al. Relationship between doppler-derived left ventricular diastolic function and exercise capacity in patients with myocardial infarction. Jpn Circ J. 65:627-31, 2001.

35. Kitzman DW, Higginbotham MB, Cobb FR, Sheikh KH, Sullivan MJ. Exercise intolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. J Am Coll Cardiol. 17:1065-72, 1991.

36. Vanoverschelde JJ, Essamri B, Vanbutsele R et al. Contribution of left ventricular diastolic function to exercise capacity in normal subjects. J Appl Physiol. 74:2225-33, 1993.

37. Douglas PS, O'Toole M. Aging and physical activity determine cardiac structure and function in the older athlete. J Appl Physiol. 72:1969-73, 1992.

38. Takemoto KA, Bernstein L, Lopez JF, Marshak D, Rahimtoola SH, Chandraratna PA. Abnormalities of diastolic filling of the left ventricle associated with aging are less pronounced in exercise-trained individuals. Am Heart J. 124:143-8, 1992.

39. Mier CM, Turner MJ, Ehsani AA, Spina RJ. Cardiovascular adaptations to 10 days of cycle exercise. J Appl Physiol. 83: 1900-1906, 1997.

40. Spina RJ, Miller TR, Bogenhagen WH, Schechtman KB, Ehsani AA. Gender-related differences in left ventricular filling dynamics in older subjects after endurance exercise training. J Gerontol A Biol Sci Med Sci. 51:B232-7, 1996.

41. Stratton JR, Levy WC, Schwartz RS, Abrass IB, Cerqueira MD. Beta-adrenergic effects on left ventricular filling: influence of aging and exercise training. J Appl Physiol. 77:2522-9, 1994.

42. Stratton JR, Levy WC, Cerqueira MD, Schwartz RS, Abrass IB. Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. Circulation. 89:1648-55, 1994.

43. Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, Lakatta EG. Left ventricular diastolic filling performance in older male athletes. JAMA. 273:1371-5, 1995.

44. Poirier P, Garneau C, Bogaty P. Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol. 85:473-7, 2000.

45. Spina RJ, Rashid S, Davila-Roman VG, Ehsani AA. Adaptations in beta-adrenergic cardiovascular responses to training in older women. J Appl Physiol. 89:2300-5, 2000.

46. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol. 140:669–682, 1994.

47. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol. 2002 Aug 7;40(3):505-10.

48. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. FASEB J. 10:615-24, 1996.

49. Turner MJ, Mier CM, Spina RJ, Schechtman KB, Ehsani AA. Effects of age and gender on the cardiovascular responses to isoproterenol. J Gerontol A Biol Sci Med Sci. 54:B393-400, 1999.

50. Hsu KL, Chiang FT, Lo HM, Tsai CH, Tseng CD, Tseng YZ. Cardiac contractility in non insulin dependent diabetes mellitus evaluated using the relation between end systolic wall stress and velocity of circumferential fiber shortening. Jpn Heart J. 38:463-71, 1997.

51. Sasso FC, Carbonara O, Cozzolino D et al. Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and non insulin dependent diabetic patients: a radionuclide ventriculographic study. J Am Coll Cardiol. 36:219-26, 2000.

52. Spina, RJ, Turner MJ, Ehsani AA. β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am J Physiol Heart Circ Physiol. 274: H397-H404, 1998.

List of Tables

Table 1. Subject characteristics prior to and following the exercise intervention

BMI = Body mass index; TC = Total cholesterol; HOMA = homeostasis model assessment of insulin sensitivity

* = $p < 0.05$ vs pre-training

Table 2. Resting hemodynamics prior to and following the exercise intervention

C_1= Large artery compliance; C_2 = Small artery compliance; SVR = systemic vascular resistance; E/A = ratio of early to late transmitral filling velocities; Pvs:Pvd = Ratio of pulmonary venous flow in systole to pulmaonry venous flow in diastole; Pva = pulmonary venous flow during atrial systole; Mad-Pad = Duration of transmitral atrial wave – duration of pulmonary venous atrial wave

* = $p < 0.05$ vs Pre

† = $p < 0.05$ vs ET

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Figure 1. Endothelial-dependent dilatation prior to and following a 10-week aerobic exercise intervention.

* = $p < 0.05$. vs pre training

Open circles = Control, Filled circles = exercise trained.

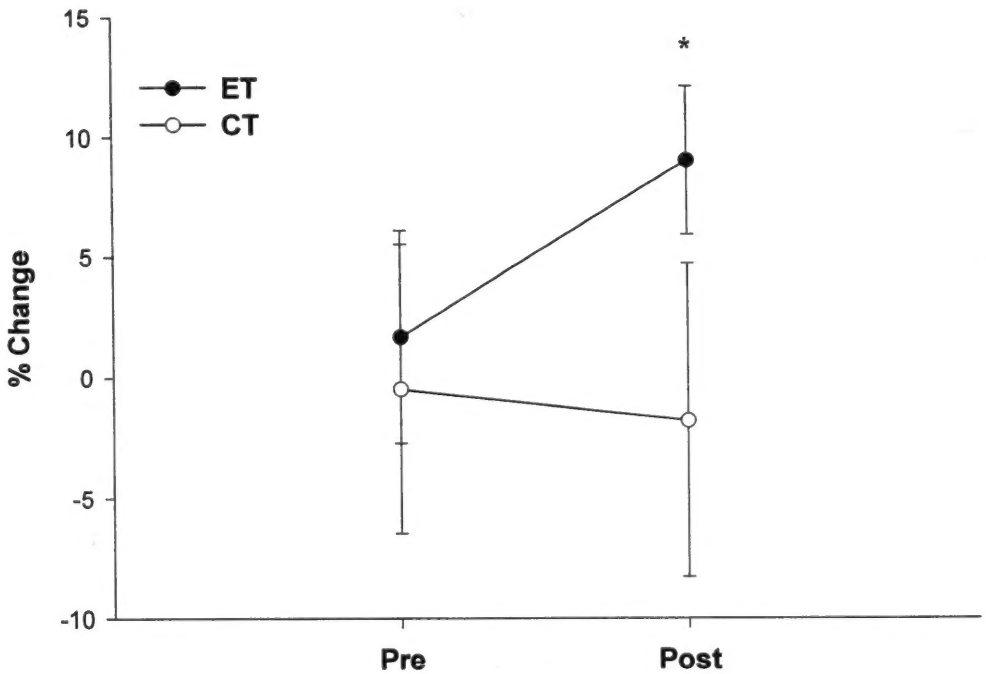
Table 1.

Variable	ET (n =7)		CT (n = 7)	
	Pre	Post	Pre	Post
Age (yrs)	59 ± 5	---	56 ± 5	---
Weight (kg)	84.6 ± 16.5	81.7 ± 19.5*	85.3 ± 20.0	85.0 ± 21.0
BMI (kg/m^2)	33.6 ± 4.7	32.5 ± 5.2	33.6 ± 4.7	33.4 ± 7.3
TC (mmol/L)	4.8 ± 0.8	5.6 ± 1.2	5.2 ± 0.8	5.0 ± 0.4
HDL (mmol/L)	1.2 ± 0.3	1.2 ± 0.1	1.3 ± 0.2	1.3 ± 0.2
LDL (mmol/L)	2.8 ± 0.8	3.5 ± 1.0	3.0 ± 0.6	2.9 ± 0.4
HbA_{1c} (%)	7.4 ± 2.0	6.9 ± 1.5	7.4 ± 1.1	7.4 ± 0.8
Glucose (mmol/L)	7.5 ± 3.0	7.9 ± 2.5	8.0 ± 0.8	7.4 ± 1.1
Insulin (mmol/L)	13.5 ± 9.4	13.2 ± 8.1	11.9 ± 5.6	13.8 ± 7.3
HOMA	4.3 ± 3.4	4.8 ± 3.8	3.75 ± 1.6	3.9 ± 2.0

Table 2.

Variable	ET (n=7)		CT (n=7)	
	Pre	Post	Pre	Post
Heart rate	71 ± 8	72 ± 7	83 ± 11	78 ± 10
SBP (mmHg)	133 ± 16	129 ± 25	139 ± 17	136 ± 20
DBP (mmHg)	75 ± 12	70 ± 7	74 ± 11	72 ± 10
VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	18.8 ± 3.5	21.6 ± 6.3*	20.02 ± 4.9	---
C_1 (mL/mmHg)	0.8 ± 0.25	0.9 ± 0.30	0.75 ± 0.23†	0.79 ± 0.29
C_2 (mL/mmHg)	0.04 ± 0.05	0.03 ± 0.01	0.03 ± 0.02	0.03 ± 0.02
SVR ($dynes \cdot sec \cdot cm^{-5}$)	1832 ± 452	1835 ± 389	1910 ± 336	1794 ± 291
E:A	0.88 ± 0.2	0.96 ± 0.07	1.03 ± 0.2	1.07 ± 0.3
Pvs:Pvd	1.61 ± 0.35	1.53 ± 0.16	1.4 ± 0.2	1.5 ± 0.2
Pva (m/s)	26.4 ± 2.0	25.9 ± 1.5	28 ± 4	29 ± 7

Figure 1.



The term "**% change**" refers to to the change in brachial artery diameter from baseline value following flow-mediated dilatation.

Chapter V
Study IV

Low Cardiorespiratory Fitness is Associated with Elevated C-Reactive protein in Women with Type II Diabetes Mellitus

INTRODUCTION

Type 2 diabetes mellitus (DM-2) is associated with an increased risk for the development of cardiovascular disease (CVD)[1] that may be explained, at least in part, by synergistic co-morbidities such as hypertension, dyslipidemia and obesity. In addition to conventional risk factors for CVD, growing evidence suggests that novel markers may play a role in determining CVD risk in patients with DM-2. These include measures of sub-acute inflammation, such as C-reactive protein (CRP)[2], vascular effects of excessive insulin[3] as well as cardiac[4] and vascular[5] maladaptations specific to DM-2.

Low cardiorespiratory fitness is associated with the increased CVD morbidity and mortality in men with and without DM-2[6]. In men with DM-2, this association remained significant after adjusting for conventional CVD risk factors such as, hypertension, dyslipidemia, smoking status and family history of CVD[6]. It is possible, however, that the adverse effects of low cardiorespiratory fitness in patients with DM-2 contribute to or exacerbate the cardiovascular[7,8] and metabolic derangements[9] that increase the risk for CVD in this population. The cardiovascular consequences of DM-2 are significantly more deleterious in females than in males[10] possibly due to gender-related differences in cholesterol profile[11] and/or significant reductions in cardiorespiratory fitness[12]. Therefore, the purpose of this investigation was to examine conventional and novel CVD risk factors in women with DM-2 stratified according to their cardiorespiratory fitness.

Methods

Thirty-two women with DM-2, free from diabetes-related complications, were screened for participation in this investigation. Presence of DM-2 was confirmed by a chart review and with fasting HbA_{1c}. Pharmacological treatment strategies for metabolic control, hypertension, dyslipidemia and preventative therapy (i.e. acetylsalicylic acid) were evenly distributed between both groups of women with DM-2 (Table 1). Groups were evenly matched for number of participants on hormone replacement therapy. Exclusion criteria for this investigation included: evidence of ischemic heart disease documented by history of CVD or by resting or exercise ECG abnormalities (>1.5 mm flat or down sloping ST segment depression); angina or any other cardiac symptoms potentially limiting exercise capacity; presence of musculoskeletal or peripheral vascular abnormalities that would limit exercise capacity. Informed consent was obtained from all

subjects prior to the investigation and the Research Ethics Review Board within the Faculty of Medicine at the University of Alberta approved the study protocol.

Study protocol

Patients reported to the Division of Cardiology, University of Alberta Hospital, for a clinical and physical examination as well as a resting and exercise electrocardiogram. A graded exercise test was performed on an electronically braked cycle ergometer to determine peak rate of consumption ($\dot{V}O_{2peak}$). On a second visit, subjects reported to the Metabolic Unit following an overnight fast for blood sampling, an assessment of arterial compliance and a resting echocardiogram. All subjects were asked to refrain from medications with vascular or cardiac effects for 48 hours prior to testing. A period of at least 48 hours separated the two visits. Subjects were than stratified into two groups according to relative $\dot{V}O_{2peak}$ values obtained from the graded maximal exercise test. The group median was used to separate participants into groups of low (LCF) and average (ACF) cardiorespiratory fitness. Eight healthy older women without DM-2 were also assessed and served as a control group.

Graded maximal exercise test

Oxygen consumption, carbon dioxide production and minute ventilation were sampled breath by breath at rest and during exercise and values were averaged every 15 seconds using a MedGraphics Metabolic Cart (Medical Graphics, Minneapolis, MN). At least two of the following criteria needed to be achieved for the determination of $\dot{V}O_{2peak}$: respiratory exchange ratio >1.10, < 100 $ml \cdot min^{-1}$ increase in $\dot{V}O_2$ for >30s despite an increase in workload, heart rate within 5 beats of age-predicted and volitional exhaustion. Arm blood pressure (auscultation) was performed according to American Heart Association guidelines and heart rate was determined from 12-lead ECG recordings.

Assessment of arterial compliance and resting hemodynamics

Arterial compliance was assessed using computerized arterial pulse waveform analysis. This technique involves 30-s recordings of signal-averaged arterial pulse waves by applanation tonometry using a surface residing pressure transducer on the radial artery

(Hypertension Diagnostics Inc., Eagan MN). Blood pressure was measured oscillometrically on the opposite arm. The diastolic decay of the waveform was analyzed mathematically and the two components of arterial compliance were calculated based on a modified Windkessel model of circulation: capacitive compliance (large artery), and oscillatory (or reflective) compliance reflecting smaller, more peripherally located arteries and arterioles. This technique has been validated previously with invasive measurements of arterial waveforms[13].

Echocardiographic Measurements.

Left ventricular imaging was performed with a commercially available ultrasound instrument (Hewlett Packard, Sonos 5500) with a 3.5 MHz transducer. Left ventricular 2-dimensional transthoracic images were obtained from the parasternal short-axis view at the level of the mid-papillary muscles according to American Society of Echocardiography guidelines[14]. Left ventricular filling dynamics were assessed using pulsed-wave Doppler analysis of transmitral and pulmonary venous flow patterns recorded in the apical four chamber view[15]. All echocardiographic images were averaged over three cardiac cycles.

Blood collection and analysis.

Blood was drawn in the fasted state prior to ultrasound imaging. Fasting haematological measurements included: glucose, insulin, HbA_{1c}, total cholesterol, HDL, triglycerides, and LDL. Insulin was measured using a Roche Diagnostics Elecsys 2010 System using the sandwich principle[16]. Glucose was measured using a hexokinase method. Total cholesterol values were obtained using a cholesterol oxidase method[17] while triglyceride values were obtained using a fully enzymatic colorimetric assay reaction for glycerol following the removal of all serum free glycerol[18]. HDL values were determined from a photometric method after the addition of PEG modified enzymes[19]. Plasma lipids, glucose and HbA_{1c} were determined on a Synchron LX20 analyzer (Beckman Coulter, Fullerton CA). Plasma CRP was analyzed using a fully automated Behring Nephelometer Analyzer System (Behring Diagnostics, Mannheim, Germany) using anti-CRP mouse monoclonal antibodies coupled to latex microparticles.

This is not an assay for high-sensitivity CRP. The homeostasis model assessment (HOMA index) was used as an estimate of insulin sensitivity[20].

Statistical Analysis

The data are presented as means ± SD. Baseline characteristics between the groups were compared using a Student's *t* test. Stepwise multiple linear regression analyses were performed to determine the relationship between $\dot{V}O_{2peak}$ and CVD risk factors. A p-value of ≤ 0.05 was considered statistically significant.

Results

Demographics and hemodynamics

Subject characteristics are provided in Table 1. Of the initial 32 women screened, four women were excluded from the investigation due to either ECG abnormalities, suggestive of underlying coronary artery disease (n=2) or failure to achieve adequate criteria for determination of $\dot{V}O_{2peak}$ (n = 2). Therefore 28 women were distributed evenly into LCF and ACF groups. Two women in each of the ACF and LCF groups and all the women in the control group were taking hormone replacement therapy. Body mass index was higher in the LCF group, due to a difference of ~10 kg (p=0.09) in body weight. No differences were observed in age or duration of diabetes between the ACF and LCF groups. The control group was significantly older than the ACF and LCF groups ($p < 0.05$). $\dot{V}O_{2peak}$ values were significantly lower in the LCF groups compared to the ACF group as per the study design. $\dot{V}O_{2peak}$ was significantly lower in the LCF groups compared to the control group. Few subjects were able to attain a respiratory exchange ratio greater than 1.10 (n=2 LCF; n=4 ACF) however average values were identical between the two groups (LCF = 1.06 ± 0.04 vs ACF = 1.06 ± 0.04). Heart rate at peak exercise was 93 ± 14 and 99 ± 9% of age predicted values in the LCF and ACF groups respectively. Taken together, these data suggest similar maximal efforts between the two groups.

There were no significant differences in resting heart rate, diastolic blood pressure and mean arterial pressure between the groups. A substantial, non-significant, difference in systolic blood pressure (146 ± 17 vs 132 ± 13 mmHg in the LCF and ACF groups respectively) was observed between the two DM-2 groups however, it did not achieve statistical significance ($p = 0.056$). No differences were observed in large or ocillatory compliance, or systemic vascular resistance, between all 3 groups.

Measures of left ventricular structure and function were similar in both DM-2 groups. Technically adequate measures of left ventricular morphology could only be obtained in 19 subjects (8 LCF and 11 ACF respectively). Although left ventricular mass indexed to body surface area tended to be higher in the LCF group (134 ± 62g/cm^2 vs 96 ± 13 g/cm^2), this difference did not reach statistical significance ($p = 0.061$). Echocardiographic analyses were not performed in healthy controls.

Haematological variables

Haematological variables are reported in Table 2. There were no differences observed in classical markers of CVD, such as total cholesterol, LDL, HDL or triglycerides between all three groups. HOMA index and HbA_{1C} was significantly higher in the LCF group compared to the control group ($p < 0.05$). CRP levels were approximately 1.5 and 3-fold higher in the LCF group compared to the control and ACF groups respectively ($p \leq 0.05$). CRP values were not different between the ACF and control group ($p \leq 0.05$). Significant negative correlations were observed between $\dot{V}O_{2peak}$ and both CRP and the HOMA index in the women with DM-2 (Figure 1). A stepwise multiple linear regression analysis between CRP and $\dot{V}O_{2peak}$, body mass index and age revealed beta values of –0.651 ($p < 0.05$), -0.216 ($p = 0.46$) and –0.203 ($p = 0.32$) respectively. Finally, we observed a significant positive correlation between the HOMA index and CRP in women with DM-2 ($r = 0.49$, $p < 0.05$, Figure 2).

Discussion

This study is the first to assess the interaction between cardiovascular fitness with conventional and novel markers of CVD risk in women with DM-2. The primary findings

of this investigation are the association of low cardiorespiratory fitness with increased HOMA index and CRP in women with DM-2. Furthermore, no relationships were observed between low cardiorespiratory fitness and classical risk factors for CVD such as: age, duration of diabetes, and lipid profile or novel risk factors such as LV filling dynamics or arterial compliance

CRP has been shown to be prospectively associated with the increased risk for the development of CVD[2] and DM-2[21]. As physical inactivity is a primary risk factor in the development of both these diseases, it is possible that this trend could be, in part, a function of reduced physical activity patterns. In support of this hypothesis, inverse associations between CRP and self-reported physical activity levels have recently been reported in multi-ethnic populations of healthy men and women[22,23]. Additionally, reports from the National Health and Nutrition Examination Survey III demonstrated that individuals who participate in vigorous exercise (> 6 metabolic equivalent levels) have a 60% reduction in CRP when compared to individuals who reported no leisure time physical activity[24]. These data suggest that increased levels of physical activity or caloric expenditure may reduce or attenuate the expression of markers of sub-clinical vascular inflammation in healthy older individuals. The data presented here support these findings and extend them to women with DM-2 as negative correlation between cardiorespiratory fitness and CRP was observed.

The mechanisms underlying the negative correlation between cardiorespiratory fitness and markers of subclinical vascular inflammation have yet to be determined, however, some evidence suggests that poor metabolic control may play a role. Firstly, prospective population-based studies have demonstrated that CRP is a strong predictor of the development of DM-2 in both genders[21]. Secondly, a recent analysis of the Women's Health Study data has demonstrated that fasting insulin levels are strongly and independently associated with CRP expression[25]. As insulin resistance precedes the development of DM-2, these observations suggest that elevated CRP expression may be secondary to reductions in insulin's metabolic actions. In line with these studies, a significant positive relationship was observed between the HOMA index and CRP in the women studied in this investigation (Figure 2).

Wei and colleagues[6] reported a 2.9-fold increased risk for all-cause mortality associated with "low fitness" (defined as the lowest quintile of ~1250 individuals) in men with DM-2 even after adjustment for conventional risk factors such as hypertension, dyslipidemia and smoking habits. The data presented here provide a possible explanation for this finding as markers of sub-clinical vascular inflammation were elevated in women with DM-2 with low cardiorespiratory fitness. Additionally, these data suggest that the increased CRP with low cardiorespiratory fitness, may be mediated through a reduction in fasting glucose control (i.e. HOMA index).

Several limitations to this investigation need to be addressed. As the sample size was less robust than larger epidemiological studies, the median value of cardiorespiratory fitness was chosen as criteria for group stratification. Had a larger sample size been evaluated and used the lowest quintile to classify "low cardiorespiratory fitness", as others have done[6,26] it is likely that much greater differences in fitness and subsequently greater differences in conventional and novel markers of CVD would have been observed.

It is also possible that these findings were a consequence of differences in body mass rather than cardiorespiratory fitness[27,28]. Inasmuch, similar to others[28] a significant relationship between the HOMA index and body mass index was observed ($r = -0.41$ $p<0.05$; data not shown), however, body mass index and CRP were unrelated ($r = 0.28$, $p=0.3$). As increased body mass has a negative impact on cardiorespiratory fitness, it is difficult to distinguish the independent effects of cardiorespiratory fitness or body mass on subclinical vascular inflammation in this investigation. To address this issue, a second analysis of the data was performed with the groups stratified according to time to exhaustion rather than cardiorespiratory fitness[6,26]. When the groups were stratified according to time to exhaustion, the differences in body mass were negated (91 ± 16 vs 89 ± 17 kg in the LCF and ACF group respectively), however the differences in CRP remained significantly different (5.9 ± 4.5 vs 2.2 ± 1.7 $g \cdot L^{-1}$).

Another limitation to this investigation is that the HOMA index is a crude estimate of insulin sensitivity, and not a direct measure of insulin-mediated glucose disposal. Despite this limitation, the relationship between $\dot{V}O_{2peak}$ and HOMA index

observed in this investigation was remarkably similar to a recent investigation that measured insulin sensitivity using the euglycemic-hyperinsulinemic clamp technique ($r = 0.42$, $p < 0.001$)[29]. Furthermore, HOMA index estimates of insulin sensitivity are closely related to measured values obtained using hyperinsulinemic-euglycemic clamp techniques (-0.796, $p < 0.0001$) in women with DM-2 [30]. As measure insulin sensitivity was not measured directly in this investigation it is unclear if low cardiorespiratory fitness is associated with a reduction in insulin sensitivity in women with DM-2, however these data suggest that it is possible.

The findings presented here have several important clinical implications. It has been suggested that the increased incidence of DM-2 and CVD in technologically advanced societies is a function of a caloric surplus due to reduced levels of physical activity[31]. Furthermore, recent evidence suggests that reduced cardiorespiratory fitness is an independent risk factor for mortality in healthy and diseased populations[6,26]. It is possible that sedentary lifestyle may lead to reduced insulin sensitivity and increased subclinical vascular inflammation, both of which are considered novel risk factors for CVD[3,14] and DM-2[21]. The observation that elevated CRP and reduced glucose control in women with DM-2 with low cardiorespiratory fitness, demonstrates the negative impact of physical inactivity on CVD risk in this population. Taken together, these data support the role of regular exercise in the prevention and treatment of metabolic and cardiovascular disorders associated with DM-2.

In conclusion, the results of the present study demonstrate that low cardiorespiratory fitness is associated with elevated CRP levels and reduced fasting glucose control in women with DM-2. Furthermore, these findings suggest that a link exists between fasting glucose control and CRP in women with DM-2.

References

1. Haffner SM, Lehto S, Ronnemma T, Pyorala K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. *N Engl J Med.* 339:229–234, 1998
2. Ridker PM, Hennekens CH, Buring JE, Rifai N: C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 342:836-43, 2000
3. Steinberg HO, Baron AD: Vascular function, insulin resistance and fatty acids. *Diabetologia.* 45:623-34, 2002
4. Taegtmeyer H, McNulty P, Young ME: Adaptation and maladaptation of the heart in diabetes: Part I: general concepts. *Circulation.* 105:1727-33, 2002
5. Lehmann ED, Gosling RG, Sönksen PH: Arterial wall compliance in diabetes. *Diabet Med* 9:114–119, 1992
6. Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med.* 132:605-11. 2000
7. Arnett DK, Evans GW, Riley WA: Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol.* 140:669–682, 1994
8. Bella JN, Palmieri V, Roman MJ Liu JE, Welty TK, Lee ET, Fabsitz RR, HowardBV, Devereux RB: Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation.* 105:1928-33, 2002
9. Després JP, Lamarche B, Mauriège P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ : Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N. Engl. J. Med.* 334:952-957, 1996
10. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA.* 265:627-31, 1991
11. Howard BV, Cowan LD, Go O, Welty TK, Robbins DC, Lee ET: Adverse effects of diabetes on multiple cardiovascular disease risk factors in women. The Strong Heart Study. *Diabetes Care.* 21:1258-65, 1998

12. Regensteiner JG, Bauer TA, Reusch JE, Brandenburg SL, Sippel JM, Vogelsong AM, Smith S, Wolfel EE, Eckel RH, Hiatt WR: Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. *J Appl Physiol*. 85:310-7, 1998
13. McVeigh GE, Bratteli CW, Morgan DJ, Alinder CM, Glasser SP, Finkelstein SM, Cohn JN: Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. *Hypertension*. 33:1392–1398, 1999
14. Sahn DJ, DeMaria A, Kisslo J, Weyman A: Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 58:1072-83, 1978
15. Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG : Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care* 24:5-10, 2001
16. Kato K, Umeda Y, Suzuki F, Hayashi D, Kosaka A: Evaluation of a solid-phase enzyme immunoassay for insulin in human serum. *Clin Chem*. 25:1306-8, 1979
17. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470-5, 1974
18. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 19(5):476-82, 1973
19. Assmann G, Schriewer H, Schmitz G, Hagele EO. Quantification of high-density-lipoprotein cholesterol by precipitation with phosphotungstic acid/MgCl2. *Clin Chem* 29:2026-30, 1983
20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412-9, 1985
21. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327-34, 2001

22. LaMonte MJ, Durstine JL, Yanowitz FG, Lim T, DuBose KD, Davis P, Ainsworth BE: Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. *Circulation* 106:403-6, 2002
23. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP: Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 153:242-50; 2001
24. Ford ES: Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 3:561-8, 2002
25. Pradhan AD, Cook NR, Buring JE, Manson JE, Ridker PM: C-reactive protein is independently associated with fasting insulin in nondiabetic women. *Arterioscler Thromb Vasc Biol.* 2003 ;23:650-5.
26. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE: Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 346:793-801, 2002
27. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 107:391-7, 2003
28. Iozzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-Jarvinen H, Ferrannini E: Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. *J Clin Endocrinol Metab* 84:863-8, 1999
29. Thamer C, Stumvoll M, Niess A, Tschritter O, Haap M, Becker R, Shirkavand F, Bachmann O, Rett K, Volk A, Haring H, Fritsche A: Reduced Skeletal Muscle Oxygen Uptake and Reduced beta-Cell Function: Two early abnormalities in normal glucose-tolerant offspring of patients with type 2 diabetes. *Diabetes Care.* 26:2126-2132, 2003
30. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in

subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23:57-63, 2000.

31. Neel JV: The "thrifty genotype" in 1998. *Nutr Rev* 57:S2-9, 1999

Tables and Figures

Table 1. Subject characteristics

Legend: BMI = Body mass index, $\dot{V}O_{2peak}$ = maximal rate of oxygen consumption C_1 = Large artery compliance, C_2 = Oscillatory compliance; SVR= Systemic vascular resistance Legend: LV = Left ventricular; LVIDd = Left ventricular internal diameter in diastole; LVMI = Left ventricular mass index; E/A ratio = ratio of early to late transmitral filling velocities; PVs; PVd; PVa = pulmonary venous flow in systole, diastole and during atrial contraction respectively; Pad-Mad = Difference between pulmonary venous and transmitral flow duration during atrial contraction.

† = $p < 0.05$ vs LCF ‡ = $p < 0.05$ vs ACF

Table 2. Hematological markers of cardiovascular disease in women with type 2 diabetes stratified according to cardiorespiratory fitness.

Legend: Hb_{A1C} = Glycosylated hemoglobin, HDL = High density lipoprotein, LDL = Low density lipoprotein, TG:HDL = Triglyceride to HDL ratio (estimate of LDL particle size)

† = $p < 0.05$ vs LCF; ‡ = $p < 0.05$ vs ACF

Figures

Figure 1. Relationship of $\dot{V}O_{2peak}$ to C-reactive protein and the HOMA index in women with type 2 diabetes.

Figure 2. Relationship between the HOMA index and C-reactive protein in women with type 2 diabetes.

Table 1.

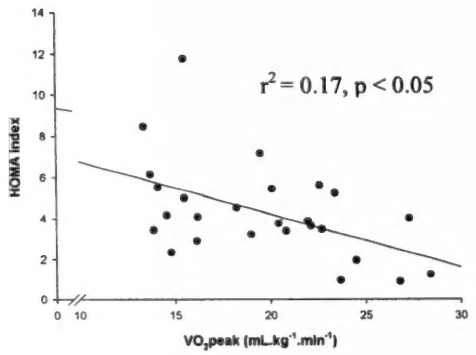
Category	Variable	LCF (n=14)	ACF (n=14)	Controls (n=8)
	Age (yrs)	59 ± 7	56 ± 5	69 ± 4†‡
Demographics	**Weight (kg)**	94.6 ± 13.1	84.4 ± 17.4	70.5 ± 10.1†‡
	BMI (kg/m^2)	37.5 ± 4.1	32.2 ± 5.6†	28.5 ± 3.7†
	Years since diagnosis	5 ± 2	4 ± 3	---
	VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.7 ± 2.0	23.2 ± 2.7†	21.9 ± 3.0†
	VO_{2peak} (% predicted)	69 ± 14	91 ± 24†	111 ± 14†
	Diabetes Therapy (D/O/I)	2/12/0	4/10/0	---
	Hypertension therapy	8	7	---
	Dyslipidemia therapy	4	4	---
Resting Hemodynamics	**HR ($beats \cdot min^{-1}$)**	76 ± 10	74 ± 11	74 ± 8
	SBP (mmHg)	146 ± 17	132 ± 13	143 ± 13
	DBP (mmHg)	78 ± 9	72 ± 12	78 ± 9
	C_1 ($mL \cdot mmHg^{-1}$)	0.82 ± 0.34	1.0 ± 0.38	0.77 ± 0.18
	C_2 ($mL \cdot mmHg^{-1}$)	0.037 ± 0.036	0.040 ± 0.033	0.022 ± 0.014
LV Morphology (n = 8 LCF group; n= 11 ACF group)	**LVIDd (cm)**	5.4 ± 1.1	4.8 ± 0.6	---
	LVMI (g/m^2)	134 ± 62	96 ± 13	---
	RWT	0.40 ± 0.05	0.40 ± 0.14	---
Estimates of LV Function	**E/A ratio**	0.95 ± 0.21	1.04 ± 0.29	---
	Deceleration time (ms)	0.24 ± 0.05	0.25 ± 0.04	---
	PVs:PVd	1.58 ± 0.28	1.48 ± 0.25	---
	Pad-Mad (s)	-27 ± 35	-33 ± 48	---
	Ejection Fraction (%)	69 ± 10	71 ± 8	---

Table 2.

Variable	LCF (n = 14)	ACF (n = 14)	Controls (n =8)
HbA_1c (%)	7.4 ± 1.7	6.9 ± 1.0	5.7 ± 0.2†
Glucose ($mmol \cdot L^{-1}$)	8.2 ± 4.0	7.5 ± 1.2	5.3 ± 0.5†
Insulin ($mU \cdot L^{-1}$)	14.7 ± 6.8	11.0 ± 6.0	6.4 ± 2.7†
HOMA index	5.3 ± 2.6	3.8 ± 2.2	1.53 ± 0.63†
Total Cholesterol ($mmol \cdot L^{-1}$)	5.3 ± 1.4	5.1 ± 0.78	5.4 ± 0.6
HDL ($mmol \cdot L^{-1}$)	1.4 ± 0.36	1.3 ± 0.21	1.7 ± 0.3
LDL ($mmol \cdot L^{-1}$)	3.1 ± 0.65	2.8 ± 0.85	3.0 ± 0.5
TG:HDL	1.9 ± 1.5	1.6 ± 0.8	0.9 ± 0.8
C-RP ($mg \cdot L^{-1}$)	6.3 ± 4.3	1.9 ± 1.7†	4.1 ± 4.0†‡

Figure 1.

(A)


HOMA index
$r^2 = 0.17$, $p < 0.05$
VO_2peak ($mL.kg^{-1}.min^{-1}$)

(B)

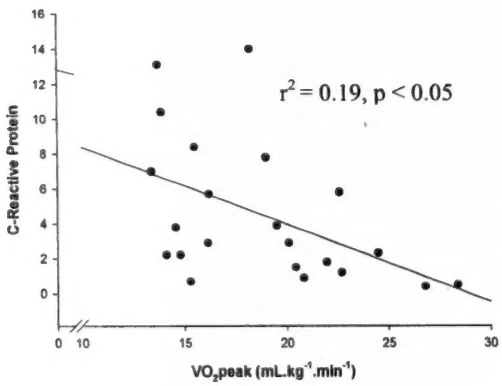
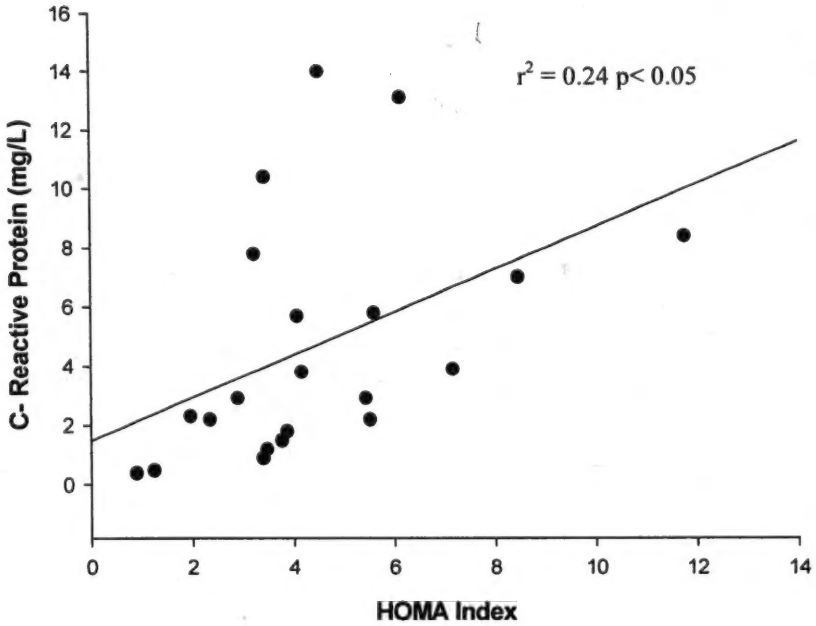

C-Reactive Protein
$r^2 = 0.19$, $p < 0.05$
VO_2peak ($mL.kg^{-1}.min^{-1}$)

Figure 2.


$r^2 = 0.24$ $p < 0.05$
C- Reactive Protein (mg/L)
HOMA Index
0
2
4
6
8
10
12
14
16

Chapter VI. DISCUSSION

Effects of exercise training on cardiovascular function

Aging and DM-2 are associated with reductions in LV and vascular structure and function that likely contribute to the increased CVD risk observed in these populations. Elevated cardiorespiratory fitness, likely attributed to increase physical activity patterns, is cardioprotective in both populations independent of conventional CVD risk factors. The purpose of these investigations was to examine the effects of an exercise intervention on cardiovascular structure and function in older women and women with DM-2.

Effects of Training on Left Ventricular Morphology

Aerobic exercise training, in the young, is typically associated with the physiological increase in LV mass, secondary to increased wall thickness and cavity dimension (i.e. the athletes heart).[1] Aging[2] and DM-2[3] are physiological conditions associated with increased LV mass and wall thickness in the sedentary state and therefore may not adapt to exercise training in the same fashion as a young healthy myocardium. A limited number of investigations have assessed the alterations in left ventricular morphology following exercise training in older populations with LV concentric hypertrophy.[4-8] These data suggest that chronic aerobic exercise training is associated with a significant regression of concentric hypertrophy. More specifically, 10-14% declines in LV mass indexed for body surface area were observed following 16-32 weeks of aerobic exercise training. These adaptations occurred secondary to reductions in interventricular and posterior wall thickness with little change in cavity area[4-8].

In Study I, at baseline LV mass in both groups was significantly higher than previously reported values[9], however, relative wall thickness and LV mass indexed to body surface area were similar to previously published investigations.[9] Similar to previous investigations[9-11] LV morphology was unaltered following exercise training in older women.

To my knowledge there have been no investigations that have examined the effects of exercise training on LV morphology in women with DM-2. At baseline the data acquired were similar to previously published values for women with DM-2[3]. In Studies II and III, LV geometry and size were unchanged following ten weeks of aerobic and strength training (Appendix Table 5). I had hypothesized that reductions in the arterial

component of afterload would improve arterio-ventricular coupling and may regress LV concentric hypertrophy. This hypothesis was based on the observation that acute improvements in arterioventricular coupling elicited favorable increases in LV function.[12-14]

In Studies II-IV, arterio-ventricular coupling was estimated from echocardiographically-derived stroke volumes coupled with arm cuff pressures. Using this method no measurable changes in arterioventricular coupling were observed following exercise training in women with DM-2. Similarly there were no differences in arterioventricular coupling between groups of type 2 diabetic women stratified according to cardiorespiratory fitness. Therefore 10-12 weeks of exercise training has negligible effects of LV morphology and arterioventricular coupling in older women with and without DM-2.

Effects of Exercise Training Left Ventricular Filling Dynamics

Left ventricular compliance is a function the ventricles ability to distend in response to changes in volume. Left ventricular relaxation is a complicated process involving active and passive mechanisms dependent upon calcium handling and structural coordinated mechanical untwisting that occurs during the relaxation of shared fibers between the left and right ventricles[15]. Accurate determination of LV compliance is difficult as it involves invasive catheterization of cardiac chambers to measure ventricular pressures coupled with simultaneous estimates of ventricular cavity dimensions. Clinically, LV compliance is assessed non-invasively by measuring blood flow velocity across the mitral valve during diastole[15,16]. The ratio of passive to active (atrial systole) filling is used a crude marker of LV compliance. A more accurate determination of LV compliance is possible by including measurements of pulmonary venous profiles throughout the cardiac cycle[15]. Although these measures do not provide true compliance values they have been shown to correlate well with invasive determination of LV pressures during diastole[16].

The purpose of Study I was to determine the effects of different modes of training (i.e. strength vs aerobic training) on cardiorespiratory fitness and left ventricular filling dynamics in older women free from cardiovascular or metabolic diseases. Due to poor

imaging quality several subjects were excluded from this portion of the investigation. The data was pooled to simply examine the role of a 12-week exercise intervention on left ventricular filling patterns in healthy older women. Similar to Spina *et al.*[9-11] left ventricular filling dynamics were unchanged despite a 15% change in $\dot{V}O_{2peak}$ following exercise training.

Several authors have demonstrated an association between LV filling and cardiorespiratory fitness (see Chapter 1 Section 3.2.2). Furthermore, both cross sectional and intervention studies have demonstrated that reductions in LV filling dynamics may be attenuated with chronic endurance exercise training (see Chapter 1 Section 3.2.2), although this is not a consistent finding[11,17]. Gender differences have been documented suggesting that the relationship between left ventricular filling dynamics and cardiorespiratory fitness may be less stalwart in women[9-11]. Data from Study I support the notion that the LV adaptation to exercise training is limited in women. Therefore the improvements in cardiorespiratory fitness may be more a function of blood flow distribution or peripheral extraction than a function of improved cardiac performance.

Studies II and III were designed to examine the cardiovascular adaptations to exercise training in women with DM-2. I chose to continue to investigate the impact of exercise training on LV filling dynamics in older women with DM-2, as Poirier and colleagues[18] had demonstrated a relationship between cardiorespiratory fitness and LV filling dynamics in normotensive men with DM-2. I therefore hypothesized that exercise training in women with DM-2 would likely enhance LV filling secondary to improvements in cardiorespiratory fitness. Similar to Study I however, no changes in LV filling dynamics or morphology were observed following a 10-week exercise intervention in women with DM-2. To my knowledge there have been no other investigations that have examined the impact of exercise training on LV filling dynamics in persons with DM-2, however these data support previous work in which exercise training was associated with minimal LV adaptation in older women[9-11].

The discrepancies between these results and those of others may be explained by the duration of the intervention or perhaps gender differences in the cardiovascular adaptation to training. It is likely the training stimulus employed may not have been of sufficient duration (10 weeks) or frequency (3 days per week) to elicit appreciable

changes in the structure or cellular properties of the LV that could be measured using Doppler-derived transmitral flow patterns. Had we continued the intervention for up to 6 months, as others have done[4-8] , it is possible that we may have produced comparable findings. Furthermore, it is clear that there is a gender-specific LV adaptation to exercise training[9-11]. Specifically, improvements in cardiorespiratory fitness with exercise training in older women seem to be more a function of an increase in arterio-venous oxygen difference, while cardiac output remains relatively unchanged[11]. The data presented here support these findings and extend them to women with DM-2.

Effects of Exercise Training on Arterial Compliance

Arterial compliance can be defined as the relationship between the changes in arterial dimension for a given change in the distending pressure[19] A negative association between arterial compliance and conventional markers of CVD, such as smoking[20], insulin resistance[21,22], dyslipidemia[23-25], and obesity[26] have been documented, suggesting that arterial compliance may be a marker of future cardiovascular events[27,28]. Recent evidence suggests a positive relationship between arterial compliance and cardiorespiratory fitness, providing evidence for a mechanism to explain the cardioprotective effects of regular physical activity (see introduction section 3.3.2).

In studies II and III diastolic pulse contour wave analysis was used to estimate arterial compliance prior to and following ten weeks of exercise training in women with DM-2. The major new finding of this investigation is that ten weeks of exercise training resulted in an improvement in arterial compliance secondary to an improvement in cardiorespiratory fitness in women with DM-2. Interestingly, these cardiovascular adaptations were observed without any appreciable change in conventional risk factors for CVD, such as blood pressure, lipid profile or insulin sensitivity.

Significant negative relationships between central arterial stiffness and $\dot{V}O_{2peak}$ have been documented in men and women[29-31]. Furthermore, arterial compliance in endurance-trained middle-aged and older men was 20% to 35% higher than their less active peers.[31] Intervention studies lasting 13-16 weeks, have demonstrated an ~20% increase in central arterial stiffness following an ~25% improvement in exercise time to exhaustion [29,31]. Similar to advancing age, DM-2 is also associated with an increase in

arterial stiffness[22]. To my knowledge these data are the first to demonstrate the beneficial effects of exercise training on arterial compliance in women with DM-2. The magnitude of change in arterial compliance following exercise traiing was in line with those observed in previous investigations that have assessed the impact of an aerobic exercise training program on arterial compliance in older healthy men and women[29-31].

As previously discussed, arterial compliance is a function of vascular structure and endothelial-mediated vascular tone (see Chapter 1 section 2.2.2). Therefore, enhanced arterial compliance with exercise training in older individuals may be explained by reductions in vascular wall thickness or improved endothelial-dependent vasodilatation[32].

It is possible that the enhanced arterial compliance following exercise training observed in Studies II and III may have been a function of an enhanced endothelial-dependent regulation of vascular tone. Exercise training has been shown to improve endothelial-dependent dilatation in older healthy individuals and persons with DM-2[33] (reviewed in Chapter 1 section 3.3.3). Specifically, eight weeks of aerobic and resistance exercise training, in type 2 diabetic patients (52 ± 2 yrs), increased flow-mediated dilatation from 1.7 to 5.0%. The data presented here in women with DM-2 show similar magnitude of improvement in endothelial dependant dilatation following exercise training.

Effects of Exercise Training on Endothelial Function

As a significant improvement in arterial compliance was observed with exercise training in women with DM-2 in study II, we sought to determine the mechanism for this improvement in study III. Endothelial-dependent regulation of vascular tone was determined by measuring brachial artery dilatation in response to shear stress created by occluding than rapidly restoring blood flow in the forearm.

The novel finding of Study III was that aerobic exercise training enhanced arterial compliance in type 2 diabetic women secondary to an improvement in endothelial-dependent dilatation. Furthermore, these alterations in vascular dynamics and function were observed despite no measurable differences in known metabolic co-variates, such

as, glycemia, advanced glycated end-products, insulin, lipids or vascular inflammatory markers.

As previously discussed, exercise training has been shown to attenuate age or diabetes/insulin resistance-related decrements in endothelial-dependent dilation (see Chapter 1 Section 3.3.3). The data presented here support the work of others who have documented improved endothelial-dependent dilatation following exercise training in patients with insulin resistance and/or diabetes (see chapter 1 section 3.3.3) The data presented here are novel in that measurements of arterial compliance were coupled with with estimates of endothelial-dependent dilatation and suggest that improvements in arterial compliance with exercise training may be a function of enhanced endothelial reactivity in women with DM-2.

The proposed mechanisms through which this enhanced vascular reactivity occurs following exercise training in women with DM-2 remains to be elucidated. Several authors have speculated exercise-mediated improved in endothelial-dependent dilatation occur secondary to improved insulin sensitivity or a reduction in oxidative stress. Although minimal changes in metabolic insulin sensitivity (i.e. HOMA index) were observed with exercise training, insulin does have vascular actions[36,37]. It is therefore possible that the exercise-training-mediated improvements in vascular function were secondary to an enhanced vascular insulin sensitivity, as this has been demonstrated in animal models[38]. Furthermore, as reactive oxygen species or by-products of oxidative stress were not determined, it is unclear whether exercise training reduced oxidative stress in the population studied. Regardless of the mechanism, the observation that exercise training elicits functional improvements in vascular compliance secondary to enhanced endothelial-dependent dilatation may explain the cardioprotective effects of enhanced cardiorespiratory fitness in persons with DM-2.

Effects of Exercise Training on Cardiorespiratory Fitness

In study I, $\dot{V}O_{2peak}$ was similar between all four groups and was equal to or slightly above the age-predicted values obtained from previously published regression formulas (Appendix Table 2). Interestingly we observed 11, 13 and 20% improvements

in $\dot{V}O_{2peak}$ in women within the aerobic-only, strength-only and aerobic and strength combined groups respectively. These data suggest that strength training is an important adjunct to the exercise training intervention in older women free from CVD. More importantly, these data suggest that the limitation to cardiorespiratory fitness in older women may be more a function of limited muscular power, and a less a function of coordinated adaptation of the cardiovascular system. It is possible that skeletal muscle force development is the "structural limitation" to exercise capacity in healthy older women. Therefore, adaptations that increase muscular force or power may lead to improvements in exercise tolerance and possibly maximal oxygen uptake in healthy older women, despite little change in cardiovascular structure or function.

A brief analysis of studies that have measured cardiorespiratory fitness prior to and following short term (< 12 weeks) exercise training interventions in persons with DM-2 reveals that the average improvement is approximately 15% (See Appendix Table 1). These data have been comprised of mainly men or mixed cohorts, therefore the female training response has yet to be intensely studied. Despite this limitation, our data are in close agreement with these previous investigations as we observed 13 and 15% improvements in VO_{2peak} following a 10-week aerobic and strength training intervention in women with DM-2.

The improvements in VO_{2peak} we observed following exercise training in Studies II and III were significantly less than the 26% improvement reported by Brandenburg and colleagues[39]. Specifically, this group reported that VO_{2peak} increased from 17.7 ± 4.0 to 22.4 ± 5.5 $ml \cdot kg^{-1} \cdot min^{-1}$ in premenopausal women with DM-2 following 12 weeks of exercise training. As the training interventions were similar between the two studies, discrepancies between the relative changes in VO_{2peak} observed following training between our investigations and that of Brandenburg *et al*[39], are likely due to differences in pre-training cardiovascular fitness. Since we did not measure cardiac output or arterio-venous oxygen difference in this investigation, we cannot speculate as to the mechanisms which could explain the increased rates of oxygen consumption following exercise training.

Correlates of Cardiorespiratory Fitness

Recently it has been shown that low cardiorespiratory fitness is associated with an increase in mortality in men with DM-2[40,41]. As novel markers of CVD were not documented in these investigations we sought to examine the impact of low cardiorespiratory fitness on LV filling dynamics and arterial compliance in women with DM-2. In Study IV, data from the 28 women studied in Studies II and III were pooled and subsequently stratified into two groups according to cardiorespiratory fitness (low and average cardiorespiratory fitness respectively). Examining the data in this way allowed us to examine the impact of low cardiorespiratory fitness on novel and conventional risk factors for CVD in women with DM-2.

The primary findings of Study IV were the association of low cardiorespiratory fitness with increased: obesity, insulin sensitivity and C-reactive protein in women with DM-2. There were also strong trends towards increased systolic blood pressure, and left ventricular mass index in women with low cardiorespiratory fitness. Furthermore, no relationships were observed between low cardiorespiratory fitness and classical risk factors for CVD such as: age, duration of diabetes, and lipid profile. Finally, no clear relationship was demonstrated between cardiovascular structure or function and low cardiorespiratory fitness in women with DM-2.

DM-2 is associated with an increased risk for the development of CVD due in part to synergistic co-morbidities such as hypertension, dyslipidemia, and obesity. However, the mechanisms underlying this association remain to be fully determined. Several possible mechanisms include the presence of sub-clinical vascular inflammation[42], hemodynamic insulin resistance[43], cardiac[3] and vascular[22] maladaptations to DM-2 or low cardiorespiratory fitness[40,41]. Wei and colleagues[41] reported a 2.9-fold increased risk for all-cause mortality associated with "low fitness" (defined as the lowest quintile of ~1250 individuals) in men with DM-2. The increased risk of mortality associated with low cardiorespiratory fitness remained significant (2.1-fold) even after adjustment for conventional risk factors such as hypertension, dyslipidemia and smoking behaviours. The investigators suggested that low cardiorespiratory fitness in men with DM-2 may be associated with poor metabolic control, which would subsequently increase their risk for CVD. Consistent with this hypothesis, we observed a negative correlation between

insulin sensitivity (assessed by HOMA index) and cardiorespiratory fitness (Chapter V, Figure 1).

C-reactive protein has been shown to be prospectively associated with the increased risk for the development of CVD[42] and DM-2[44]. Inverse associations between C-reactive protein and self-reported physical activity levels have recently been reported in multi-ethnic populations of healthy men and women[45,46]. Additionally, reports from the National Health and Nutrition Examination Survey III demonstrated that individuals who participate in vigorous exercise (> 6 metabolic equivalent levels) displayed a 60% reduction in C-reactive protein when compared to individuals who reported no leisure time physical activity[46]. These data suggest that increased levels of physical activity may reduce or attenuate the expression of markers of sub-clinical vascular inflammation in healthy older individuals. Our data support these findings as we observed a significant negative correlation between cardiorespiratory fitness and C-reactive protein in our sample of women with DM-2 (Chapter V, Figure 1). Furthermore, we also observed a positive correlation between insulin sensitivity and C-reactive protein in women with DM-2 (Chapter V, Figure 2). Our data reflect a possible interrelationship between low cardiorespiratory fitness, reduced insulin sensitivity and elevated markers of subclinical inflammation, thereby supporting past findings and extending them to the population of women with DM-2. Interestingly, we did not observe any changes in C-reactive protein with exercise training in studies II or III.

The mechanisms underlying the negative correlation between cardiorespiratory fitness and markers of subclinical vascular inflammation have yet to be determined, however, some evidence suggests that poor metabolic control may play a role. Firstly, prospective population-based studies have demonstrated that C-reactive protein is a strong predictor of the development of DM-2 in both genders[44]. Secondly, a recent analysis of the Women's Health Study data has demonstrated that fasting insulin levels are strongly and independently associated with C-reactive protein expression[47]. As insulin resistance precedes the development of DM-2, these observations suggest that elevated C-reactive protein expression may be secondary to reductions in insulin's metabolic actions. In line with these investigations, we observed a significant relationship between the HOMA index and C-reactive protein (Chapter V, Figure 2). This finding was

surprising as our sample consisted exclusively of women with severe insulin resistance. It is therefore possible that a reduction in insulin sensitivity associated with low cardiorespiratory fitness may be one of the mechanisms through which C-reactive protein expression is increased in sedentary or less physically fit individuals, even within cohorts of patients with DM-2.

Potential Mechanisms

Several co-morbidities associated with both aging and DM-2 have an impact of both arterial and left ventricular compliance, such as obesity, hypertension, hyperlipidemia and insulin resistance.

Since we did observe significant differences in body mass with exercise training (Study II&III) or by study design (Study IV) our results may be related to changes or differences in body composition as we observed significant differences in body mass index between the participants in the low and average cardiorespiratory fitness groups. Body composition could have effected our results as obesity is associated with, increased circulating free fatty acids[48], elevated circulating adipocytokines[49] and/or subsequent reductions in insulin sensitivity[50]. Furthermore, several investigators have demonstrated the impact of obesity on LV filling dynamics[51-54] and arterial compliance[26] however few studies have been performed to determine the effects of weight loss on either of these parameters in persons with DM-2. Although we did observe a significant relationship between body mass index and insulin sensitivity, body mass index was not related to LV filling dynamics or arterial compliance when all subject-data were pooled and analysed. Therefore, the impact of obesity on the cardiovascular determinants measured in these investigations was limited.

It is possible that differences in fat mass or adipocyte function may have influenced our results. The impact of obesity on non-adipocyte cellular function is far more intricate than once believed[55]. The discovery of cytokines that are released from adipocytes and have peripheral action[55] , for example the derivative of the *ob* gene, leptin[56] suggest that the adipocyte may act as a organ with the capacity to sense and respond to altered physiological states[55]. For example, postprandially, the adipocyte will respond to elevations in blood glucose and circulating free fatty acids by releasing

adipocytokines which have an effect on peripheral insulin sensitivity[57,58]. Since there is a close relationship between adiposity and atherosclerosis several authors have hypothesized that, similar to insulin, adipocytokines may have vascular as well as metabolic actions[58-61]. Leptin receptors have been discovered on smooth muscle cells[62] and leptin has also been shown to induce nitric-oxide dependent vasodilatation in peripheral[59,61] and coronary arteries[63]. Recent data suggest that leptin may also regulate arterial compliance[64], therefore it is possible that changes in arterial compliance we observed following exercise training may have been mediated through an enhanced leptin sensitivity or a reduction in circulating leptin concentrations.

Similarly, insulin has been shown to enhance vascular compliance and increase blood flow in conduit and resistance blood vessels[36,37,48]. Recent investigations suggest that obesity-mediated metabolic insulin resistance is coupled with a resistance to insulin's vascular actions[36,37,48]. Exercise training has been shown to improve metabolic insulin sensitivity irrespective of weight loss[65,66]. It is therefore possible that exercise training may also elicit improvements in vascular insulin sensitivity as well. In support of this hypothesis, 14 days of treadmill running improved insulin-mediated capillary recruitment in male Wistar rats despite no change in capillary density or basal femoral blood flow[38]. The authors concluded that peripheral vascular insulin sensitivity increased in conjunction with metabolic insulin sensitivity following exercise training. As metabolic insulin sensitivity increased slightly in Studies II and III following exercise training, it is possible that exercise-mediated improvements in arterial compliance were achieved through an enhanced vascular insulin sensitivity.

Finally, there is a wide body of evidence which suggests that ectopic lipid deposition or steatosis causes cellular dysfunction and accelerates apoptosis, in skeletal[67], cardiac[68] and vascular smooth muscle[69]. Interventions that increase lipid oxidation such as metformin[70], or re-distribute lipid stores to adipocytes such as PPARγ-agonists[71] have been shown to have a favorable impact on both metabolic[70] and cardiovascular function[68,72-74]. The beneficial cardiovascular outcomes associated with these metabolic interventions are likely mediated through improved lipid metabolism. It is possible that differences in arterial compliance or metabolic insulin sensitivity may have been mediated through improved lipid metabolism following exercise training.

Exercise training has been shown to elicit similar beneficial metabolic outcomes, which seem to be mediated through the activation and increased expression of the enzyme AMP-activated protein kinase (AMPK)[75]. AMPK activation regulates glucose homeostasis by activating GLUT-4 translocation[76] and subsequent glucose transport into the cell[77] as well as lipid homeostasis by increasing lipid oxidation[78]. Increased lipid oxidation with exercise training is likely achieved through AMPK-mediated reductions in malonyl-CoA derived inhibition of carnitine palmitoyl transferase-1[78-80]. It is possible that exercise mediated activation of AMPK with muscular contraction, has an anti-steatotic effect in persons with DM-2.

Interestingly, it has recently been demonstrated that AMPK is activated in non-exercising tissues following 30 minutes of running in rats[80]. It has been suggested that AMPK activation may occur in the endothelium following exercise training and may enhance vascular function, possibly through reductions in vascular smooth muscle triglyceride content[81]. AMPK activation could therefore explain the improved endothelial reactivity observed following exercise therapy in persons with DM-2. It is possible that the enhanced endothelial reactivity associated with exercise training we observed in our investigation was secondary to AMPK-mediated improvements in insulin sensitivity and/or direct AMPK activation in the endothelium.

Clinical Implications

Impaired LV filling dynamics and reduced arterial compliance are associated with an increased CVD risk in men and women with and without DM-2[82,83]. Reduced LV filling dynamics associated with DM-2[84] and aging [85] may simply reflect the LV adaptation to altered loading conditions due to changes in LV morphology or vascular compliance. The clinical concern associated with reduced LV filling dynamics is the development of diastolic heart failure, the prevalence of which has been estimated to be upwards of 57% of heart failure cases[86]. Although exercise training was not associated with enhanced LV filling dynamics in our studies, several studies have demonstrated that exercise training or high cardiorespiratory fitness is associated with improved LV diastolic function (see chapter 1 section 3.2.2) Longer interventions with more intense or rigorous exercise training regimes are likely necessary to elicit measurable changes in LV

filling in older or DM-2 populations. Recently, invasive measurements of LV compliance have been performed in older athletic and sedentary individuals[87]. Data suggest that chronic intense exercise training for prolonged periods attenuate the age-associated decline in LV compliance. Therefore, enhanced LV compliance may be a mechanism through which exercise training mediates protection from the development of cardiovascular disorders in the elderly. To date, however, the impact of prolonged exercise interventions on LV compliance in persons with DM-2 has yet to be studied. Our data suggest that a 10- or 12-week exercise intervention is insufficient to elicit measurable changes in LV filling dynamics in women with or without DM-2.

Since up to 80% of all deaths in persons with DM-2 may be attributed to some type of cardiovascular disorder[88], interventions that ameliorate the risk for the development of CVD are paramount in the treatment of these patients, especially women[16 - 89]. Increased arterial stiffness has been identified as independent modifiable risk factor in the development of CVD[27,28]. In these investigations a brief exercise intervention in women with DM-2 enhanced arterial compliance, and thereby possibly reducing the risk for CVD-related morbidity and mortality. More importantly, these adaptations occurred despite little or no change in blood pressure, cholesterol profile or insulin sensitivity. It is therefore possible to observe a cardiovascular adaptation to a lifestyle intervention, despite no measurable changes in conventional markers of CVD risk. Therefore, non-invasive determination of arterial compliance may be an important tool clinically to assess the efficacy of treatment in addition to the conventional assessment of CVD risk[90].

Finally, insulin resistance and vascular inflammation have recently been accepted as novel risk factors for the development of CVD[91] and DM-2[44]. Furthermore, reduced rates of physical activity are associated with increased sub-clinical vascular inflammation[45,46] and insulin resistance[65]. Conversely, increased physical activity patterns, even in high-risk populations have been shown to improve insulin sensitivity[65,66] and reduce the expression of vascular inflammatory markers[45,46]. In this investigation low cardiorespiratory fitness was associated with increased vascular inflammation and reduced insulin sensitivity in a population at high risk for CVD. It is likely that sedentary lifestyle, even in high-risk populations, leads to reduced insulin

sensitivity and increased subclinical vascular inflammation, both of which are considered novel risk factors for CVD[42,91]. The observation that elevated C-reactive protein and reduced insulin sensitivity in women with DM-2 who have low cardiorespiratory fitness, demonstrates the negative impact of physical inactivity in this population. Taken together, these data support the role of regular exercise in the prevention and treatment of metabolic and cardiovascular disorders associated with DM-2.

Study Limitations

A few limitations to our investigations need to be addressed. In Studies I-III LV and arterial function were not assessed during physiological stress such as exercise or β-adrenergic stimulation. Therefore it is unclear if exercise training elicited improvements in inotropic or lusitropic reserve in these populations. Several investigations have demonstrated impaired inotropic responsiveness in both older healthy[92] and type 2 diabetic individuals[93,94]. Furthermore, improved inotropic reserve with endurance exercise training has been documented in healthy older men[92]. Although it is possible that the improvements in cardiorespiratory fitness observed in studies I-III were a function of enhanced LV inotropic reserve, it would appear that this adaptation is limited to males.

Baseline differences in arterial compliance were observed in Study III, despite similar patient demographics in both groups. It is possible that these differences were a function of menopausal status. As menopausal status was determined from self-report, it is unclear which participants were in the perimenopause from those in true menopause. The perimenopause is a transitional phase of the ovarian cycle during which estrogen levels fluctuate on a less frequent basis than during a normal ovarian cycle. As estrogen has known vascular effects[95], it is possible that the baseline differences in larger artery compliance were a function of differences in estrogen status between the two groups. Finally, the poor adherence within the intervention groups significantly reduced statistical power and limited the ability to describe cardiovascular adaptations to training in women with DM-2. To control for these limitations a minimal criteria of 80% adherence to the intervention was set for data to be included in the final analysis. Therefore, despite the

low adherence I believe that the changes observed with training are specific to the imposed intervention.

In study III, although demographics were similar between both groups at baseline, there was a significant difference in large artery compliance between the two groups. As co-variates for arterial compliance such as age, body mass and cardiorespiratory fitness were not different between the groups we cannot explain why these differences occurred. Although it is possible that these differences may have affected the final results, as compliance was greater in the ET group prior to the intervention, one would expect that group to have less reserve relative to the group with lower compliance at baseline. It is therefore unlikely that these baseline differences did not contribute to the observed changes in compliance following exercise training.

CONCLUSIONS

In conclusion, enhanced cardiorespiratory fitness following exercise training in women with type 2 diabetes was associated with enhanced larger artery compliance and endothelial-dependent dilatation despite no change in left ventricular filling dynamics or conventional CVD risk factors. Additionally, low cardiorespiratory fitness in women with type 2 diabetes, is associated with elevated C-reactive protein and insulin resistance, independent of conventional risk factors for CVD.

FUTURE DIRECTIONS

The cardiovascular maladaptations associated with age and DM-2 have been poorly described as they have only recently begun to impact health care systems. Recent evidence suggests that these maladaptations are perhaps more a function of reduced physical activity patterns rather than a distinct feature of either condition. As such exercise training has the potential to attenuate or perhaps regress the adverse changes in cardiovascular structure and function in these individuals. Further studies are required to describe the role of exercise in preventing cardiovascular disorders associated with aging and DM-2.

There is currently a growing body of research describing the effects of exercise training on cardiovascular structure and function in older individuals, however few data are currently available on individuals with DM-2. Future research in this area should be designed to elucidate the cellular mechanisms regulating cardiac and vascular function in individuals with DM-2, and the mechanisms through which exercise training modulates their regression. These studies must be done with a large randomized clinical trial and a large prospective cross sectional analysis between individuals with high and low cardiorespiratory fitness and DM-2. Furthermore, an accurate description of the rate of decline in cardiac and vascular structure following the onset of diabetes should be properly described.

Finally, a larger clinical emphasis should be placed on the cardiovascular consequences associated with age and DM-2 and treatments should be aimed at attenuating deleterious changes in cardiac and vascular structure and function in these populations. Exercise is a key intervention in the prevention of cardiovascular dysfunction and should therefore be recognized to a greater extent in clinical settings.

REFERENCES

1. Pluim BM, Zwinderman AH, van der Laarse A, et al. The athlete's heart. A meta-analysis of cardiac structure and function. Circulation. 2000;101:336-44.

2. Gerstenblith G, Frederiksen J, Yin FC, et al. Echocardiographic assessment of a normal adult aging population. Circulation. 1977;56:273-8.

3. Devereux RB, Roman MJ, Paranicas M et al. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation. 2000;101:2271-6.

4. Kokkinos PF, Narayan P, Colleran JA et al. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. N Engl J Med. 1995;333:1462-7.

5. Turner MJ, Spina RJ, Kohrt WM et al. Effect of endurance exercise training on left ventricular size and remodeling in older adults with hypertension. J Gerontol A Biol Sci Med Sci. 2000;55:M245-51.

6. Baglivo HP, Fabregues G, Burrieza H et al. Effect of moderate physical training on left ventricular mass in mild hypertensive persons. Hypertension. 1990;15:I153-6.

7. Wirth A, Kroger H. Improvement of left ventricular morphology and function in obese subjects following a diet and exercise program. Int J Obes Relat Metab Disord. 1995;19:61-6.

8. Hinderliter A, Sherwood A, Gullette EC et al. Reduction of left ventricular hypertrophy after exercise and weight loss in overweight patients with mild hypertension. Arch Intern Med. 2002;162:1333-9.

9. Spina RJ, Rashid S, Davila-Roman VG et al. Adaptations in beta-adrenergic cardiovascular responses to training in older women. J Appl Physiol. 2000;89:2300-5.

10. Spina, RJ, Miller TR, Bogenhagen WH et al. Gender-related differences in left ventricular filling dynamics in older subjects after endurance exercise training. J Gerontol A Biol Sci Med Sci 1996;51:B232-B237.

11. Spina RJ, Ogawa T, Kohrt WM, Martin WH 3rd, Holloszy JO, Ehsani AA. Differences in cardiovascular adaptations to endurance exercise training between older men and women. J Appl Physiol. 1993;75:849-55.

12. Chen CH, Nakayama M, Talbot M, Nevo E, Fetics B, Gerstenblith G, Becker LC, Kass DA. Verapamil acutely reduces ventricular-vascular stiffening and improves aerobic exercise performance in elderly individuals. J Am Coll Cardiol. 1999;33:1602-9.

13. Petrella RJ, Nichol PM, Cunningham DA, Paterson DH. Verapamil improves left ventricular filling and exercise performance in hypertensive and normotensive elderly individuals. Can J Cardiol. 1994;10:973-81.

14. Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. J Am Coll Cardiol. 1999;33:1567-72.

15. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. Circulation. 1984 Jan;69(1):190-6.

16. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation. 2002, 19;105:1387-93.

17. Fleg JL, Shapiro EP, O'Connor F, Taube J, Goldberg AP, Lakatta EG. Left ventricular diastolic filling performance in older male athletes. JAMA. 1995;273:1371-5.

18. Poirier P, C Garneau P, Bogaty P et al. Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. Am J Cardiol. 2000; 85:473-7.

19. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, Ganz P. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. Hypertension. 2001;38:1049-53.

20. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. Hypertension. 2003;41(1):183-7.

21. Salomaa V, Riley W, Kark JD, et al. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation. 1995;91:1432-43.

22. Lehmann ED, Gosling RG, Sonksen PH. Arterial wall compliance in diabetes. Diabet Med. 1992;9:114-9.

23. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, Frenneaux MP, Cockcroft JR. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. J Am Coll Cardiol. 2002;39(6):1005-11.

24. Shige H, Dart A, Nestel P. Simvastatin improves arterial compliance in the lower limb but not in the aorta. Atherosclerosis. 2001;155:245-50.

25. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, Kingwell BA. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol. 2002;39:1020-5.

26. Giltay EJ, Lambert J, Elbers JM, Gooren LJ, Asscheman H, Stehouwer CD. Arterial compliance and distensibility are modulated by body composition in both men and women but by insulin sensitivity only in women. Diabetologia. 1999;42:214-21.

27. Arnett DK, Evans GW, Riley WA: Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol. 1994; 140:669–682.

28. Hodes RJ, Lakatta EG, McNeil CT. Another modifiable risk factor for cardiovascular disease? some evidence points to arterial stiffness. J Am Geriatr Soc. 1995; 43:581–582.

29. Cameron JD, Rajkumar C, Kingwell BA et al. Higher systemic arterial compliance is associated with greater exercise time and lower blood pressure in a young older population. J Am Geriatr Soc. 1999;47:653-6.

30. Vaitkevicious PV, Fleg JL, Engel JH et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation. 1993;88:1456–1462.

31. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. Arterioscler Thromb Vasc Biol. 1998;18:127–132.

32. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation. 2003;107:139-46.

33. Maiorana A, O'Driscoll G, Cheetham C et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol. 2001, 38:860-6.

34. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37:1344-50.

35. Vaitkevicius PV, Lane M, Spurgeon H, Ingram DK, Roth GS, Egan JJ, Vasan S, Wagle DR, Ulrich P, Brines M, Wuerth JP, Cerami A, Lakatta EG. A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Proc Natl Acad Sci U S A. 2001;98:1171-5.

36. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent. A novel action of insulin to increase nitric oxide release. J Clin Invest. 1994;94:1172-9.

37. Westerbacka J, Vehkavaara S, Bergholm R, Wilkinson I, Cockcroft J, Yki-Jarvinen H. Marked resistance of the ability of insulin to decrease arterial stiffness characterizes human obesity. Diabetes. 1999;48:821-7.

38. Rattigan S, Wallis MG, Youd JM, Clark MG. Exercise training improves insulin-mediated capillary recruitment in association with glucose uptake in rat hindlimb. Diabetes. 2001;50:2659-65.

39. Brandenburg SL, Reusch JE, Bauer TA et al. Effects of exercise training on oxygen uptake kinetic responses in women with type 2 diabetes. Diabetes Care. 1999;22:1640-6.

40. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793-801.

41. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med. 2000;132:605-11.

42. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.

43. Tamminen M, Westerbacka J, Vehkavaara S, Yki-Jarvinen H. Insulin-induced decreases in aortic wave reflection and central systolic pressure are impaired in type 2 diabetes. Diabetes Care. 2002;25:2314-9.

44. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001;286:327-34.

45. Church TS, Barlow CE, Earnest CP, Kampert JB, Priest EL, Blair SN. Associations between cardiorespiratory fitness and C-reactive protein in men. Arterioscler Thromb Vasc Biol 2002;22:1869-76.

46. Ford ES. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology. 2002;3:561-8.

47. Pradhan AD, Cook NR, Buring JE, Manson JE, Ridker PM. C-reactive protein is independently associated with fasting insulin in nondiabetic women. Arterioscler Thromb Vasc Biol. 2003 ;23:650-5.

48. Steinberg HO, Baron AD. Vascular function, insulin resistance and fatty acids. Diabetologia. 2002;45:623-34.

49. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, Arita Y, Kihara S, Matsuzawa Y. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med. 1999;38(2):202-6.

50. Iozzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-Jarvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab. 1999;84:863-8.

51. Alpert MA, Terry BE, Mulekar M et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol. 1997;80:736-40.

52. Mureddu GF, de Simone G, Greco R et al. Left ventricular filling pattern in uncomplicated obesity. Am J Cardiol. 1996;77:509-14.

53. Nagano N, Nagano M, Yo Y et al. Role of glucose intolerance in cardiac diastolic function in essential hypertension. Hypertension. 1994; 23:1002-5.

54. Seto S, Kapuku GK, Kawahara , et al. Influence of mild to moderate obesity on left ventricular stress filling pattern in hypertension. Hypertens Res. 1998;21:245-50.

55. Fruhbeck G, Gomez-Ambrosi J, Muruzabal FJ, Burrell MA. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. Am J Physiol Endocrinol Metab. 2001;280:E827-47.

56. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425-32.

57. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995;270:26746-9.

58. Shimabukuro M, Koyama K, Chen G, Wang MY, Trieu F, Lee Y, Newgard CB, Unger RH. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. Proc Natl Acad Sci U S A. 1997;94:4637-41.

59. Nakagawa K, Higashi Y, Sasaki S, Oshima T, Matsuura H, Chayama K. Leptin causes vasodilation in humans. Hypertens Res. 2002;25:161-5.

60. Kimura K, Tsuda K, Baba A, Kawabe T, Boh-oka S, Ibata M, Moriwaki C, Hano T, Nishio I. Involvement of nitric oxide in endothelium-dependent arterial relaxation by leptin. Biochem Biophys Res Commun. 2000;273:745-9.

61. Lembo G, Vecchione C, Fratta L, Marino G, Trimarco V, d'Amati G, Trimarco B. Leptin induces direct vasodilation through distinct endothelial mechanisms. Diabetes. 2000;49:293-7.

62. Sierra-Honigmann MR, Nath AK, Murakami C, Garcia-Cardena G, Papapetropoulos A, Sessa WC, Madge LA, Schechner JS, Schwabb MB, Polverini PJ, Flores-Riveros JR. Biological action of leptin as an angiogenic factor. Science. 1998;281(5383):1683-6.

63. Matsuda K, Teragawa H, Fukuda Y, Nakagawa K, Higashi Y, Chayama K. Leptin causes nitric-oxide independent coronary artery vasodilation in humans. Hypertens Res. 2003;26:147-52.

64. Singhal A, Farooqi IS, Cole TJ, O'Rahilly S, Fewtrell M, Kattenhorn M, Lucas A, Deanfield J. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? Circulation. 2002;106:1919-24.

65. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med. 1998;49:235-61.

66. Ivy JL, Zderic TW, Fogt DL. Prevention and treatment of non-insulin-dependent diabetes mellitus. Exerc Sport Sci Rev. 1999; 27:1-35.

67. Roden M, Price TB, Perseghin G, Petersen KF, Rothman DL, Cline GW, Shulman GI. Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest. 1996;97:2859-65.

68. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A. 2000;97:1784-9.

69. Ross, R. Cell biology of atherosclerosis. Annu. Rev. Physiol. 1995;57: 791-804.

70. Zhou G, Myers R, Li Y, Chen Y, Shen X, Fenyk-Melody J, Wu M, Ventre J, Doebber T, Fujii N, Musi N, Hirshman MF, Goodyear LJ, Moller DE. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001;108:1167-74.

71. Yamauchi T, Kamon J, Waki H, Murakami K, Motojima K, Komeda K, Ide T, Kubota N, Terauchi Y, Tobe K, Miki H, Tsuchida A, Akanuma Y, Nagai R, Kimura S, Kadowaki T. The mechanisms by which both heterozygous peroxisome proliferator-activated receptor gamma (PPARgamma) deficiency and PPARgamma agonist improve insulin resistance. J Biol Chem. 2001;276:41245-54.

72. Hirayama H, Sugano M, Abe N, Yonemoch H, Makino N. Troglitazone, an antidiabetic drug, improves left ventricular mass and diastolic function in normotensive diabetic patients. Int J Cardiol. 2001;77:75-9.

73. Mather KJ, Verma S, Anderson TJ. Improved endothelial function with metformin in type 2 diabetes mellitus. J Am Coll Cardiol. 2001;37:1344-50.

74. Caballero AE, Saouaf R, Lim SC, Hamdy O, Abou-Elenin K, O'Connor C, Logerfo FW, Horton ES, Veves A. The effects of troglitazone, an insulin-sensitizing agent, on the endothelial function in early and late type 2 diabetes: a placebo-controlled randomized clinical trial. Metabolism. 2003;52:173-80.

75. Winder WW. Energy-sensing and signaling by AMP-activated protein kinase in skeletal muscle. J Appl Physiol. 2001;91:1017-28.

76. Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, Winder WW. 5' AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. Diabetes. 1999;48:1667-71.

77. Musi N, Hayashi T, Fujii N, Hirshman MF, Witters LA, Goodyear LJ. AMP-activated protein kinase activity and glucose uptake in rat skeletal muscle. Am J Physiol Endocrinol Metab. 2001;280:E677-84.

78. Vavvas D, Apazidis A, Saha AK, Gamble J, Patel A, Kemp BE, Witters LA, Ruderman NB. Contraction-induced changes in acetyl-CoA carboxylase and 5'-AMP-activated kinase in skeletal muscle. J Biol Chem. 1997;272:13255-61.

79. Wojtaszewski JF, MacDonald C, Nielsen JN, Hellsten Y, Hardie DG, Kemp BE, Kiens B, Richter EA. Regulation of 5'AMP-activated protein kinase activity and substrate utilization in exercising human skeletal muscle. Am J Physiol Endocrinol Metab. 2003;284:E813-22.

80. Park H, Kaushik VK, Constant S, Prentki M, Przybytkowski E, Ruderman NB, Saha AK. Coordinate regulation of malonyl-CoA decarboxylase, sn-glycerol-3-phosphate acyltransferase, and acetyl-CoA carboxylase by AMP-activated protein kinase in rat tissues in response to exercise. J Biol Chem. 2002;277:32571-7.

81. Ruderman NB, Cacicedo JM, Itani S, Yagihashi N, Saha AK, Ye JM, Chen K, Zou M, Carling D, Boden G, Cohen RA, Keaney J, Kraegen EW, Ido Y. Malonyl-CoA and AMP-activated protein kinase (AMPK): possible links between insulin resistance in muscle and early endothelial cell damage in diabetes. Biochem Soc Trans. 2003;31(Pt 1):202-6.

82. Bella JN, Palmieri V, Roman MJ et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. Circulation. 2002;105:1928-33.

83. Hodes RJ, Lakatta EG, McNeil CT. Another modifiable risk factor for cardiovascular disease? some evidence points to arterial stiffness. J Am Geriatr Soc. 1995; 43:581–582.

84. Liu JE, Palmieri V, Roman MJ et al. The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. J Am Coll Cardiol. 2001;37:1943-9.

85. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev. 1993;73:413-67.

86. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289:194-202.

87. Levine et al, MSSE(2003) abstract.

88. Haffner SM, Lehto S, Ronnemma T et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. N Engl J Med 1998, 339:229–234.

89. Barrett-Connor EL, Cohn BA, Wingard DL et al. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991;265:627-31.

90. O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. Hypertension. 1990;15:339-47.

91. Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ. Hyperinsulinemia as an independent risk factor for ischemic heart disease. N Engl J Med. 1996;334:952-7.

92. Spina, RJ, Turner MJ, Ehsani AA. β-Adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am J Physiol Heart Circ Physiol. 1998;274: H397-H404.

93. Hsu KL, Chiang FT, Lo HM et al. Cardiac contractility in noninsulin dependent diabetes mellitus evaluated using the relation between endsystolic wall stress and velocity of circumferential fiber shortening. Jpn Heart J. 1997;38:463-71.

94. Sasso FC, Carbonara O, Cozzolino D et al. Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. J Am Coll Cardiol. 2000;36:219-26.

95. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. FASEB J. 1996;10:615-24.

APPENDICES

Table 1.

Investigation	n (m/f)	Age (yrs)	BMI (Mean)	Training				$\dot{V}O_{2peak}$ (ml·kg·min^{-1})		
				F-D	I	D	Type	Pre	Post	% Change
Ruderman et al, 1979[110]	6/0	44± 11	29.2 ± 2.1	5d/wk 24 ± 4 wk	NR	24-30	CE	24.5 ± 1.8	28.0 ± 2.0*	↑ 14%
Bogardus et al, 1984[111]	2/8	44± 11	NR	3d/wk 12 wk	75% HR max	20-30	Aerobic	37.0 ± 0.9	41.8 ± 0.9*∂	↑ 13%
Schneider et al, 1984[112]	20/ 0	51 ± 2	NR	3d/wk 6wk	70-75% VO_2max	47 min	Aerobic	26.2 ± 1.1	28.4 ± 1.0	↑ 8%
Trovati et al, 1984[113]	5/0	54 ± 4	NR	7d/wk 6 wk	50-60% VO_2max	60	CE	2018 ± 98 mL/min	2342 ± 107 mL/min	↑ 15%
Reitman et al, 1984[114]	3/3	26 ± 8	NR	5-6 d/wk 6-10 wk	60-90% of VO_2max	20-40	Aerobic Interval	40.0 ± 2.0	~46.8*∂	↑ 17%
Ronnemaa et al, 1986[115]	13?	53	NR	5-7 d/wk 16 wk	70% of VO_2max	45	Aerobic	26.7 ± 6.5	29.3 ± 6.2*	↑ 10%

Lampman et al, 1987[116]	19/ 0	49 ± 2	25.9 ± 0.8	3 d/wk 9 wk	85% HR max	30-40	Jogging	29.7 ± 1.0	34.2 ± 1.4*	↑ 15%
Skarfors et al, 1987[117]	6/0	59 ± 1	25.4 ± 3.2	2d/wk 2 yrs	75% VO_2max	45	Aerobic	2100 ± 267 mL/min	2430 ± 300* mL/min	↑ 16%
Rogers et al, 1988[118]	10/ 0	53 ± 3	30.3	7d/wk 1 wk	68± 1% VO_2max	50-60	TM & CE	25.9 ± 1.0	26.9 ± 1.2	↑ 4%
Ronnemaa et al, 1988[119]	15/ 10	52.5	NR	5-7 d/wk 16 wk	~70% VO_2max	>45	Walking/ jogging	26.7 ± 1.8	29.3 ± 1.7*	↑ 10%
Segal et al, 1991[120]	6/0	36 ± 2	35.5	4d/wk 12 wk	70% VO_2max	70	CE	1626 ± 78 mL/min	2242 ± 85* mL/min	↑ 25%
Schneider et al, 1992[121]	142 32	55 ± 1	27.1 ± 0.4	3-4 d/wk 12wk	65-75% HRR	40-60	Aerobic	24.5 ± 0.7	No change	---
Dela et al, 1994[122]	7/0	58 ± 2	29.1 ± 0.3	5d/wk 9wk	~70% 1-legged VO_2max	30 min	CE	28.1 ± 2.1	30.7 ± 1.5*	↑ 9%

Smutok et al, 1994[123]	8/0	53 ± 6	28.7	3d/wk2 0wk	60-85% HRR	40 min	TM	31.0 ± 7.9	36.6 ± 6.8*	↑ 18%
Lehmann et al, 1995[124]	8/8	54	31.2 ± 7.5	4d/wk 12 wk	50-70% VO_2max	30-45	Aerobic	NR	NR	↑ (% NR)
Poirier et al, 1996[125]	11/ 0	48	NR	3d/wk 24 wk	60% $V0_2$max	30-60	CE	32.2 ±1.2	38.0 ± 1.7*	↑ 18%
Dunstan et al, 1997[126]	9/3	53 ± 7	29.7 ± 4.3	3d/wk 8wk	HR<100 bpm	10	CE & stretching	22.6 ± 4.7	No change	0.2± 7%
	8/3	52 ± 8	29.1± 2.4		50-65% VO_2max	40	CE	22.3 ± 3.1	~ 24.8	↑ 11± 8%
Ligtenberg et al, 1997[127]	10/ 20	63 ± 3	30.8 ± 4.0	3d/wk 12wk#	60-80% VO_2max	60	Aerobic	21.0 (SD NR)	21.0 (SD NR)	↔
Mourier et al, 1997[128]	20/ 4	45 ± 2	30.4 ± 1.6	3d/wk 8wk	75% VO_2max **	45	CE	23.0 ± 1.2	32.4 ± 1.3*	↑ 41%

Eriksson et al, 1998[129]	3/4	60 ± 5	28.4 ± 0.9	3d/wk 10 wk	60% HR max	60-90	Aerobic & CE	21.6 ± 1.9	25.4 ± 2.4*	↑ 18%
Brandenburg et al, 1999[130]	0/8	43 ± 7	31.8 ± 6.5	3d/wk 12 wk	70-85% HRmax	60	Aerobic	17.7 ± 4.0	22.4 ± 5.5*	↑ 27%
Tessier et al, 2000[131]	7/12	69 ± 4	30.7 ± 5.4	3d/wk 16wk	50-74% VO_2max	50	Aerobic/ CWT	423 ± 207 sec$	471 ± 230 sec*	↑ 11%*
Rigla et al, 2001[132]	9/4	56 ± 5	26.6 ± 3.6	3d/wk 12 wk	60-75% VO_2max	50-60	CE	25.2 ± 4.5	26.9 ± 3.8	↑ 7%

d/wk = days per week; n = sample size; BMI = body mass index (kg/m^2); either calculated from data presented or mean reported by authors; NR = Not reported

BMI: Standard deviations provided when reported, otherwise means were calculated from data provided

Training: F-D = Frequency and duration of the exercise program; I = Intensity of the prescribed exercise; D = Duration of each individual exercise session; VO_2max = maximal aerobic power;

HR = Heart rate; HRR = Heart rate reserve; TM = Treadmill, CE = Cycle ergometry; CWT = Circuit weight training; Aerobic = Prescribed aerobic exercise such as a combination of walking, cycling, hiking, running, skiing ect.

∂ = VO_2 reported as ml/kg FFM/min

** = Training included one session per week of interval training which was prescribed at 5 sets of 2 minutes intervals at 85% of VO_{2peak} interspersed with 3 minutes of recovery at 50% of VO_{2peak}.

= initial 6 weeks of training was supervised, followed by 6 weeks of unsupervised home-based training.

$ = Cardiovascular fitness reported as increase time to exhaustion during maximal test

? = no reference made to gender

Table 2. Subject characteristics for all studies

Variable	Healthy Older	Study I		Study II	Study III		Study IV	
	Control	ET	CT	ET	ET	CT	LCF	ACF
n	8	20	7	10	7	7	14	14
Age (yrs)	69 ± 4	69 ± 4	67 ± 4	56 ± 4	59 ± 5	56 ± 5	59 ± 7	56 ± 5
Height (m)	1.60 ± 0.05	1.62 ± 0.07	1.62 ± 0.05	1.61 ± 0.06	1.59 ± 0.04	1.58 ± 0.07	1.59 ± 0.05	1.62 ± 0.08
Weight (kg)	70.5 ± 10.1	71.3 ± 14.9	75.3 ± 11.6	95.4 ± 12.1	84.6 ± 16.5	85.3 ± 20.0	94.6 ± 13.1	85.3 ± 20.0
BMI (kg/m^2)	28.5 ± 3.7	27.3 ± 5.2	28.7 ± 4.6	35.9 ± 4.2	33.6 ± 7.3	33.6 ± 4.7	37.5 ± 4.1	33.6 ± 4.7
HRT (n)	6	10	3	4	0	0	---	---
$\dot{V}O_{2peak}$ (%predicted)	111 ± 14	109 ± 14	105 ± 15	82 ± 15	78 ± 14	82 ± 20	69 ± 14	91 ± 24*

BMI = body mass index; HRT = hormone replacement therapy

Table 3. Baseline haematological variables prior to and following training in all studies

Variable	Healthy older	Study II		Study III				Study IV	
	Controls	Pre Training	Post Training	ET - Pre	ET - Post	CT - Pre	CT - Post	LCF	ACF
HbA_{1C} (%)	5.7 ± 0.2	6.7 ± 1.1	6.6 ± 0.9	7.4 ± 2.0	6.9 ± 1.5	7.4 ± 0.77	7.4 ± 1.5	7.4 ± 1.7	6.9 ± 1.0
Cholesterol ($mmol \cdot L^{-1}$)	5.4 0.6	5.4 ± 1.5	5.5 ± 1.6	4.8 ± 0.8	5.6 ± 1.2	5.2 ± 0.77	5.0 ± 0.4	5.3 ± 2.6	3.8 ± 2.2
LDL ($mmol \cdot L^{-1}$)	3.0 ± 0.5	1.28 ± 0.2	1.30 ± 0.3	2.8 ± 0.8	3.5 ± 1.0	3.0 ± 0.6	2.9 ± 0.4	5.3 ± 1.4	5.1 ± 0.78
HDL ($mmol \cdot L^{-1}$)	1.7 ± 0.31	2.9 ± 1.0	2.8 ± 0.8	1.16 ± 0.14	1.2 ± 1.0	1.4 ± 0.23	1.3 ± 0.2	1.4 ± 0.36	1.3 ± 0.21
Triglycerides ($mmol \cdot L^{-1}$)	1.4 ± 0.9	2.8 ± 2.1	2.8 ± 1.8	4.2 ± 6.0	2.1 ± 0.9	1.8 ± 0.73	1.6 ± 0.6	2.37 ± 1.98	1.93 ± 0.72
HDL:TG	0.88 ± 0.79	2.3 ± 1.5	1.8 ± 0.92	1.7 ± 0.62	1.9 ± 0.1	1.3 ± 0.6	1.3 ± 0.7	3.1 ± 0.65	2.8 ± 0.85
Glucose ($mmol \cdot L^{-1}$)	5.3 ± 0.5	7.6 ± 1.8	8.1 ± 1.9	7.5 ± 3.0	7.9 ± 2.5	8.0 ± 0.8	7.4 ± 1.1	8.2 ± 4.0	7.5 ± 1.2
Insulin ($mU \cdot L^{-1}$)	6.4 ± 2.7	14.1 ± 6.6	13.2 ± 6.6	13.5 ± 9.4	13.2 ± 8.1	11.9 ± 5.6	13.8 ± 7.3	14.7 ± 6.8	11.0 ± 6.0
HOMA	0.88 ± 0.79	5.1 ± 2.7	4.6 ± 2.9	4.3 ± 3.4	4.8 ± 3.8	4.2 ± 1.8	4.4 ± 2.3	1.9 ± 1.5	1.6 ± 0.8
CRP ($g \cdot L^{-1}$)	4.1 ± 4.0	N/A	N/A	5.4 ± 4.8	7.8 ± 6.8	2.8 ± 1.9	2.7 ± 2.1	6.3 ± 4.3	1.9 ± 1.7

Table 4. Baseline hemodynamics prior to and following training in all studies

	Healthy Older	Study II		Study III				Study IV	
Variable	Controls	Pre Training	Post Training	ET - Pre	ET – Post	CT - Pre	CT - Post	LCF	ACF
Heart rate (bpm)	74 ± 8	75 ± 12	72 ± 14	71 ± 8	72 ± 7	83 ± 11	78 ± 10	76 ± 10	74 ± 11
SBP (mmHg)	143 ± 13	143 ± 15	137 ± 15	133 ± 16	129 ± 25	139 ± 17	136 ± 20	146 ± 17	132 ± 13
DBP (mmHg)	78 ± 9	81 ± 6	77 ± 12	75 ± 12	70 ± 7	74 ± 11	72 ± 10	78 ± 9	72 ± 12
C_1 (mL/mmHg)	0.77 ± 0.18	1.03 ± 0.46	1.22 ± 0.41*	0.80 ± 0.25	0.90 ± 0.30	0.75 ± 0.23	0.80 ± 0.29	0.82 ± 0.34	1.0 ± 0.38
C_2 (mL/mmHg)	0.022 ± 0.014	0.047 ± 0.04	0.035 ± 0.01	0.043 ± 0.053	0.025 ± 0.007	0.029 ± 0.18	0.03 ± 0.01	0.037 ± 0.036	0.040 ± 0.033
SVR	2142 ± 285	1800 ± 418	1587 ± 210*	1832 ± 452	1835 ± 389	1910 ± 336	1809 ± 268	1787 ± 363	1913 ± 396
E (m/s)	---	87 ± 8	83 ± 13	89 ± 18	92 ± 14	96 ± 23	91 ± 22	97 ± 14	85 ± 15
A (m/s)	---	90 ± 23	84 ± 16	104 ± 28	96 ± 18	83 ± 11	87 ± 23	106 ±21	84 ± 15
E/A	---	1.03 ± 0.29	1.01 ± 0.21	0.88 ± 0.17	0.96 ± 0.07	1.03 ± 0.22	1.07 ± 0.26	0.95 ± 0.21	1.04 ± 0.29
PVs:PVd	---	1.49 ± 0.17	1.38 ± 0.23	1.61 ± 0.35	1.53 ± 0.16	1.42 ± 0.23	1.51 ± 0.08	1.58 ± 0.28	1.48 ± 0.25
Pva (m/s)	---	28.5 ± 7.7	29.8 ± 5.2	26.4 ± 2.0	25.9 ± 1.5	28.2 ± 3.8	29.2 ± 7.0	27.6 ± 4.6	29.1 ± 5.6
VO_{2peak} (L/min)	1.53 ± 0.21	1.81 ± 0.32	1.93 ± 0.33*	1.67 ± 0.40	1.61 ± 0.24	1.84 ± 0.54*	---	1.48 ± 0.23	1.83 ± 0.56*
VO_{2peak} ($mL/kg \cdot min^{-1}$)	21.9 ± 3.0	19.9 ± 4.3	22.1± 5.0*	18.8 ± 3.5	21.6 ± 6.3*	20.0 ± 4.9	---	15.7 ± 2.0	23.2 ± 2.7*

SBP/DBP = Systolic and diastolic blood pressure; C_1 & C_2= large and small artery compliance; SVR = systemic vascular resistance; E & A= early and late (atrial) phases of transmitral filling; PVs/PVd/PVa = pulmonary venous flow during left ventricular systole, the early phase of left ventricular filling, and retrograde flow during atrial systole; VO_{2peak} = peak rate of oxygen comsumption. * = $p < 0.05$ vs baseline

Table 5. Left ventricular geometry and function prior to and following training in all studies

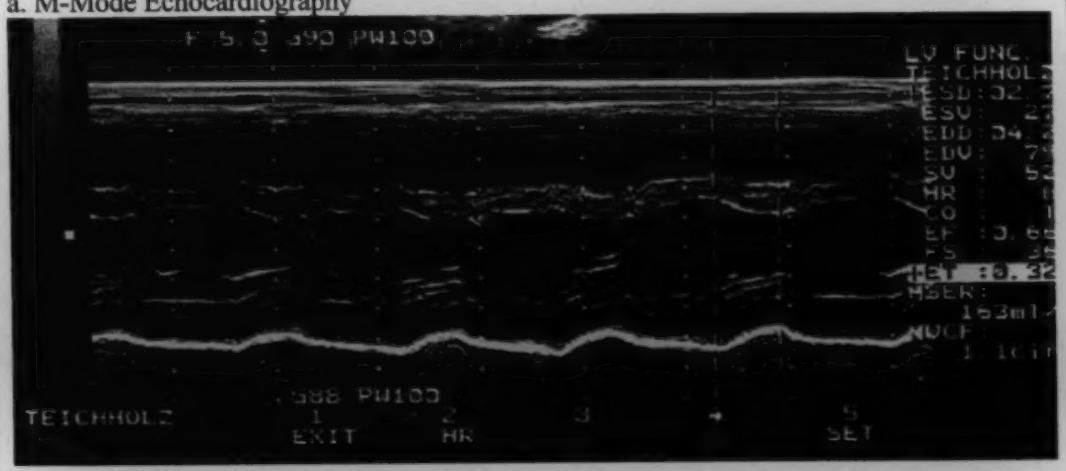
	Study I				Study IV		Study II-III Combined			
	ET (n= 18)		CT (n= 7)		n = 8	n = 11	ET (n=9)		CT (n=5)	
Variable	Pre	Post	Pre	Post	LCF	ACF	Pre	Post	Pre	Post
LVM (g)	135 ± 25	144 ± 41	168 ± 23	158 ± 49	268 ± 132	188 ± 31.5	130 ± 56	115 ± 51	174 ± 28	181 ± 29
LVMI (g/m^2)	77 ± 12	81 ± 14	66 ± 15	90 ± 27	134 ± 62	96 ± 13	256 ± 120	219 ± 108	91 ± 9	100 ± 13
RWT	0.40 ± 0.06	0.38 ± 0.08	0.41 ± 0.06	0.44 ± 0.07	0.40 ± 0.05	0.41 ± 0.14	0.44 ± 0.10	0.41 ± 0.08	0.39 ± 0.13	0.39 ± 0.08
LVIDd (mm)	44.2 ± 4.9	46.2 ± 5.2	45.0 ± 3.7	43.9 ± 6.1	53.5 ± 10.6	48.4 ± 5.8	51.4 ± 10.6	49.2 ± 9.2	46.6 ± 2.7	48.4 ± 4.0
LVIDs (mm)	24.3 ± 3.4	25.6 ± 3.7	23.4 ± 2.1	24.7 ± 5.3	32.3 ± 7.0	28.8 ± 5.4	28.6 ± 7.0	27.8 ± 6.8	30.0 ± 4.3	30.2 ± 3.8
PWTd (mm)	8.7 ± 1.3	8.5 ± 1.0	9.2 ± 1.2	9.4 ± 0.7	10.6 ± 1.4	9.6 ± 2.5	1.10 ± 0.2	0.99 ± 0.17	0.90 ± 0.23	0.93 ± 0.15
IVSd (mm)	8.3 ± 1.5	8.1 ± 1.3	9.9 ± 1.0	9.3 ± 1.2	9.8 ± 1.5	9.0 ± 1.2	0.99 ± 0.10	1.01 ± 0.20	0.92 ± 0.15	0.91 ± 0.08
Ea	---	---	---	---	1.7 ± 0.6	1.8 ± 0.4	1.67 ± 0.56	1.85 ± 0.62	2.08 ± 0.32	1.75 ± 0.42
Ees	---	---	---	---	4.2 ± 2.9	4.7 ± 2.0	5.42 ± 2.53	5.00 ± 1.73	4.20 ± 2.12	3.75 ± 1.25
Ea/Ees	---	---	---	---	0.48 ± 0.22	0.43 ± 0.16	0.35 ± 0.15	0.41 ± 0.23	0.56 ± 0.19	0.49 ± 0.11
EF (%)	77.9 ± 0.08	82.2 ± 0.11	76.3 ± 0.04	75.9 ± 0.07	68 ± 10	71 ± 8	75± 8	74 ± 9	65 ± 8	68 ± 5

LVM = Left ventricular mass, LVMI = LVM indexed for body surface area ; RWT = relative wall thickness ; LVID= left ventricular internal diameter at end systole and diastole respectively ; PWT = posterior wall thickness ; IVS = interventricular spetal wall thickness ; Ea = end systolic arterial elastance ; Ees = end systolic elastance (SBP/LVIDs) ; EF = ejection fraction

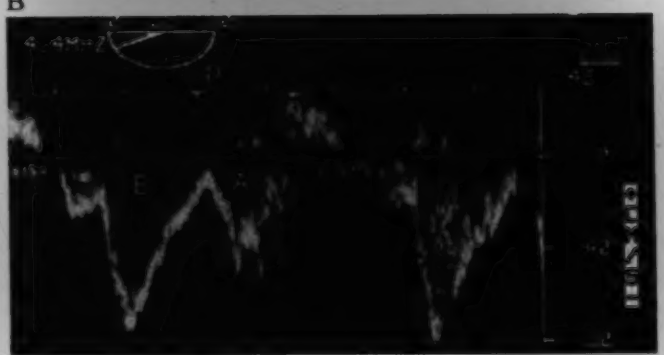
Figure 1. Graphic Representation of the Pulse Wave Analysis.

Figure 2. Typical images obtained from ultrasound determination of cardiac structure and function.

a. M-Mode Echocardiography



Doppler Ultrasound a = Pulmonary venous flow profiles; b= transmitral flow profiles

A

B